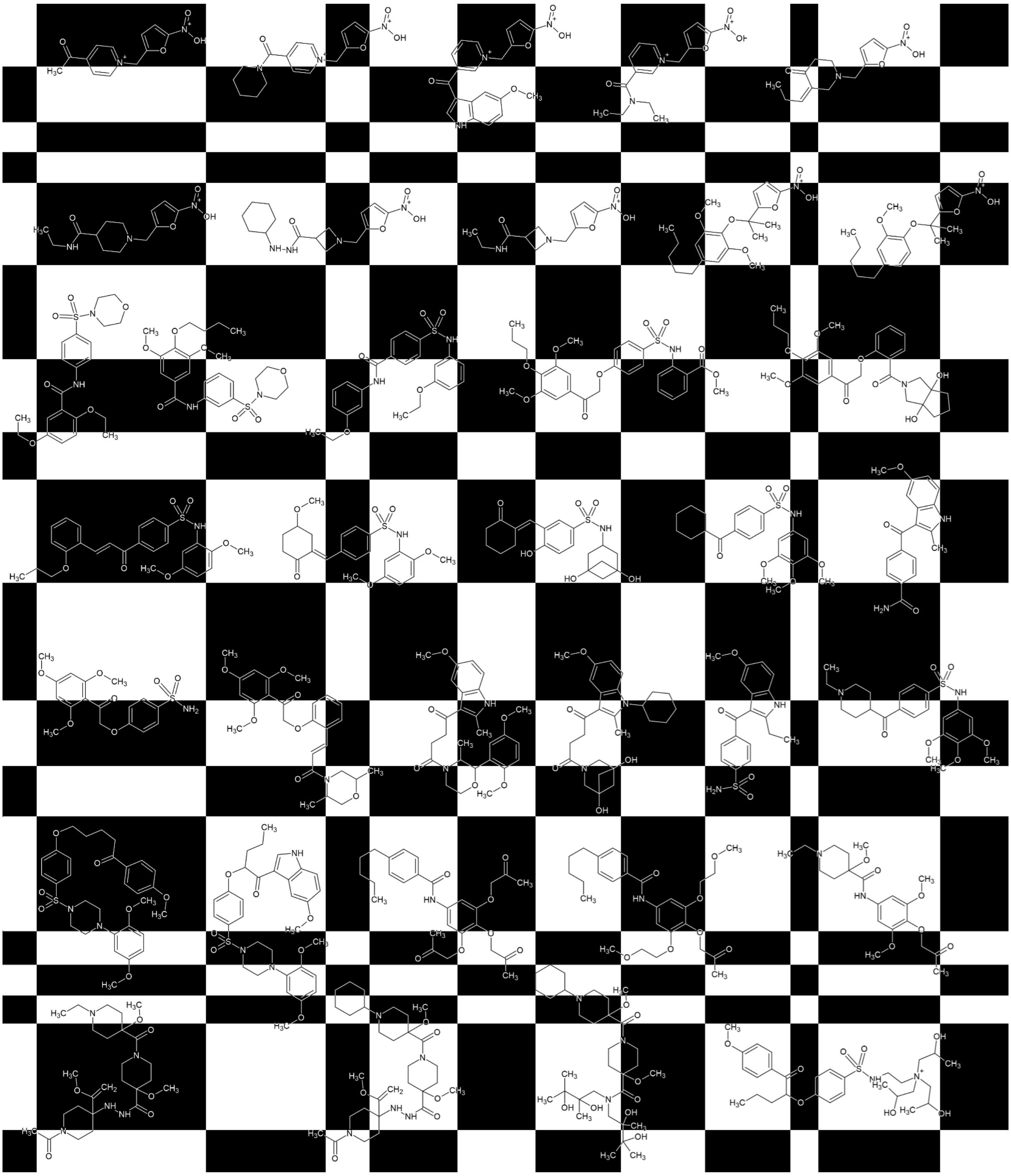
# Monograph. Pharmacology, Rational Drug Design, Independent Research Works and Projects.

Independent researcher Yaroslav Grigorievich Zaitsev(Nabrosov) 0000-0002-0069-2997



A book of collected works and publications of the author, 2004–2025.

The purpose of the publication is to implement the most important projects, such as non-narcotic anticancer cannabinoids of various physicochemical and pharmacological groups, and antibiotics with a fundamentally new strategy for implementing antibiotic action, antibiotics of the post-micromycete era. As well as a number of other projects in the field of pharmacology, light industry, food and agricultural industries.

The author does not have a scientific degree, and has been conducting independent research activities since 2004. Has a higher education as a certified specialist in the field of pharmacological and biotechnological industries, worked as an organic synthesis chemist in several laboratories. The main type of employment is research.

The author practically does not refer to  references, since the author's works are often innovative, and the official requirements for compiling works do not correspond to the very essence of the author's works. The author also does not waste time writing extensive works, since most of the author's time and effort is spent on achieving a result or overcoming the path from the unknown to the discovery.

Since the author's goals are extremely pragmatic, the style of presentation of the material is similar to that which is more often stored in the safe of a pharmaceutical company than in an official scientific paper; it is an internal workshop directive written in a popular science style of presentation.

The author wrote a paper on synthetic pro-cannabinoid anticancer anthocyanins, probably before a similar group of substances was found in plant materials, the author was the first in the world to publish a pharmacological scheme of picrocrocin (the active substance of Crocus Sativus).

A brief digression, I know it's hard to believe. This is a book about science, you can always check it if you master the material. Tell me, which of the two teachers is the real one, the one who had great teachers or the one who didn't have any at all? I don't know what "real" means to you, but I can definitely tell you who was the First.

The author was the first to publish a paper on ultra-light cannabinoids (much weaker than marijuana), the first to publish a pharmacological scheme of alpha-terpineol and amantadine. The author was the first to publish examples of anti-cancer cannabinoids that do not pass the blood-brain barrier.

The first to publish a paper on the pseudo-complex behavior of affinity molecules on biopolymers. The first to outline a theoretical path to post-micromycete antibiotics, using pseudo-complex multi-component substances and irreversible denaturation of the main pathogen protein as an example.

Despite such a high declared track record and such high goals, the author's works have a number of shortcomings, these are often inaccuracies in punctuation and different styles of presentation of visual material. Such shortcomings are due to the fact that the works were translated from their native language using Google Translate, and in different periods of time.

Also, the main disadvantage of the work of an independent researcher today is the difficulty in setting up studies.

The latter significantly narrows the experimental part of the work. The author, of course, was engaged in research and received certain results, tested completely new substances, structures of a completely new design, new cores, new tactics and strategies of drug design.
Such studies were carried out mainly in relation to light drugs, such as physiologically active alcohols, also high-affinity derivatives of new drug design cores and some others.

The results obtained served as a compass for the formation of unique methods of drug design, new approaches and the discovery of unknown groups of substances, the formation of a theoretical basis for the development of completely new strategies of drug design.

I hope to get a lot of your precious time, and I hope for a great result. We will implement all priority projects, improve the connection between pharmacology and society. The specialty of drug designer will become less private and rare, pharmacology will have more feedback.

My works, notes on materials, as well as feedback in professional and social networks:
Academy https://independent.academia.edu/YaroslavZaitsev
LinkedIn https://www.linkedin.com/in/yaroslav-zaitsev-58218bb9
YouTube https://www.youtube.com/@Drug_Design_Nabrosov
X https://x.com/nabrosov
Telegram https://t.me/DrugDesignHyperPharma
E-mail nabrosovnabrosov@gmail.com

## Sections.

1. Non-narcotic anti cancer cannabinoids.. pp. 4-33
2. Post-microbiological antibiotics and bioavailable complex bioactive structures. pp. 34-44
3. Pharmacology and drug design, new structures, pharmacological schemes of substances, drug projects, as well as inclusion of such topics as microbiology, genetics, light industry.. pp. 47-114

## Part one.

Non-narcotic, anti-cancer cannabinoids..

1. Popular science about the design of anti cancer cannabinoids. p. 4

2. Rational design anticancer cannabinoids, based on quaternary ammonium bases that do not cross the blood-brain barrier. p. 12.

3. Peripherally Selective bioavailable Cannabinoid Receptor Type 1. Peripheral (CB1) Antagonists and (CB2) Agonists. Rational Design. p. 16

4. New pharmacological cores of GPR55 Receptor Antagonists and Agonists. Rational Drug Design, small molecules. p. 19

5. CBD, highly active, pharmacological derivatives. p. 27

6. The biosynthesis of the cannabinoids CBDH, CBDP, THCH, THCP. p. 30

7.Glutamic acid derivatives as anticancer agents. p. 32

# Popular science about the design of anti cancer cannabinoids.

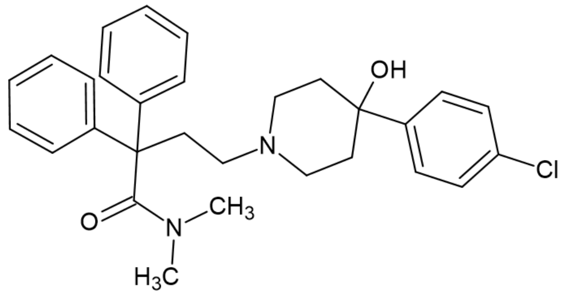
My name is Yaroslav, I am an independent researcher and drug developer, more than 15 years ago I picked up a feather pen to start drawing my first drafts of drugs. It was one of the projects touching on unexplored areas of pharmacology. Shedding light on such areas is my job, I dedicate all my time to it.

Let's take a closer look at a more recent topic, the project of non-narcotic cannabinoids.
The narcotic effects of cannabinoids put the staff of clinics, pharmacological companies, law enforcement agencies, and parents of patients into a difficult position.
The anticancer mechanisms of cannabinoids have been discovered not so long ago, mainly cannabinoids have an anticancer effect by increasing specific immunity, since CB2 and GPR55 receptors are closely related to immunity, and reducing inflammatory effects - CB1 antagonists and some others.

Some additional synergistic effects are also possible, associated with their terpene structure or pro alkaloid structure, in particular in the case of substances based on quaternary ammonium salts. Quaternary ammonium salts often exhibit a sterilizing effect and chemotherapeutic activity in relation to rapidly dividing cells, as do some phenols, terpenes and alkaloids. This allows their additional anticancer properties to manifest, since cancer cells also divide quickly and consume many substances, without which they quickly lose viability, this makes them related to microbial cells.

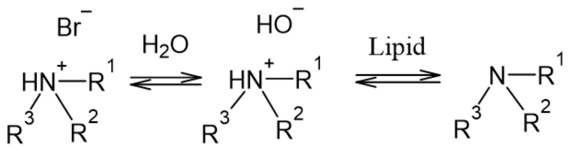
Thus, we open the door to a rich world of physical, chemical and pharmacological properties of small molecules, where the simplest structure of an anti-cancer cannabinoid can exhibit anti-cancer properties in areas such as: chemotherapeutic action, pro-apoptosis action, blocking nuclear processes, blocking transport processes, changing membrane polarity, sorption on cell membranes, influence on proliferation, regulation of inflammatory processes and, of course, powerful activation of specific anti-cancer immunity.

Is it possible to get rid of the narcotic effect of powerful cannabinoids? The central effects of cannabinoids are the only limiting factor for the clinical use of such drugs. By removing the central activity and getting safe drugs for billions of people on the planet? Yes, and this has not been a trick for a long time, here is a drug that is probably familiar to everyone, it is Loperamide, a non-narcotic powerful opiate:

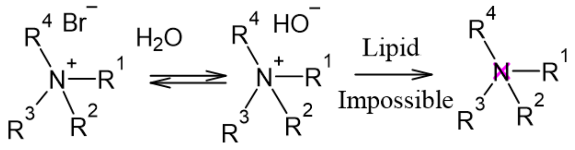


Loperamide is related to methadone, N-phenethyl-nor-pethidine and fentanyl, but it has a very spacious globular structure with special radicals, so it is poorly absorbed from the stomach and is almost not psychoactive, since it does not penetrate the blood-brain barrier.

There are other examples, quaternary ammonium bases, such as methylnaltrexone and many others. Quaternary ammonium bases are always polar, and this dramatically reduces penetration through the walls of the gastrointestinal tract, biomembranes and the blood-brain barrier:



Tertiary ammonium bases, polar and non-polar.

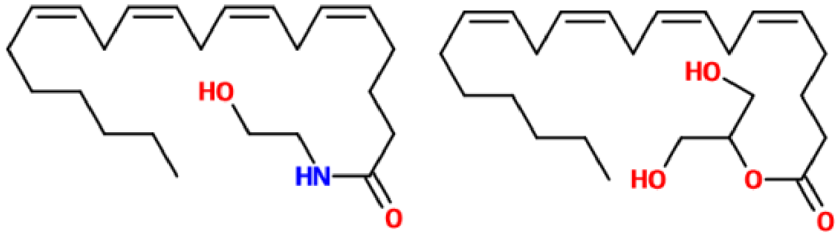


Quaternary ammonium bases, always polar.

Doesn't get into the brain - means it doesn't have a narcotic effect. For example, when we're scared, our body releases a lot of adrenaline, and adrenaline can be taken orally, like dopamine, but without noticeable narcotic effects, since these molecules are too hydrophilic and for this reason don't get into the brain. But if they passed the blood-brain barrier, then a fatal outcome from an overdose would be guaranteed.

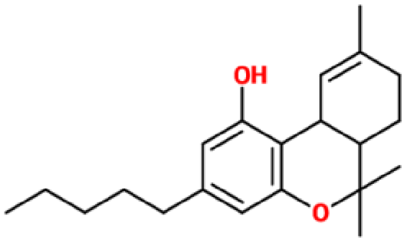
I've been developing proterpene substances for many years. I tested some substances on myself as a guinea pig. These were adaptogens, substances close to the active substances of ginseng, rose rhodiola, echinacea.. But there were also examples of highly active cannabinoids of a completely unique design. I think it won't be difficult for me to draw hundreds of completely new types of cannabinoids.

Let's start with a few examples, a few new nuclei, with different chemical and pharmacological properties that differ significantly from endogenous cannabinoids:

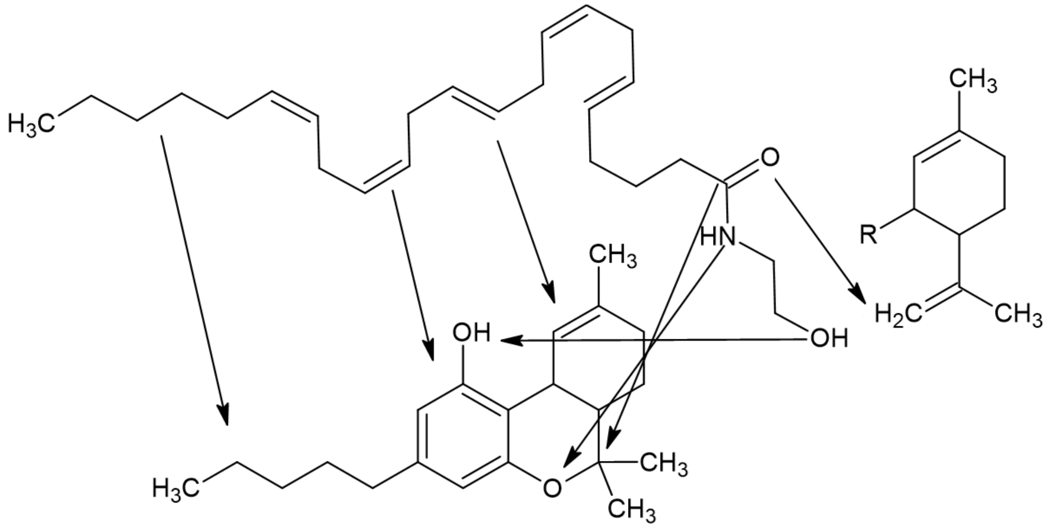


Anandamide 2-AG

Endogenous cannabinoids, conditionally biolabile.



THC lipophilic, centrally active terpenoid natural cannabinoid.

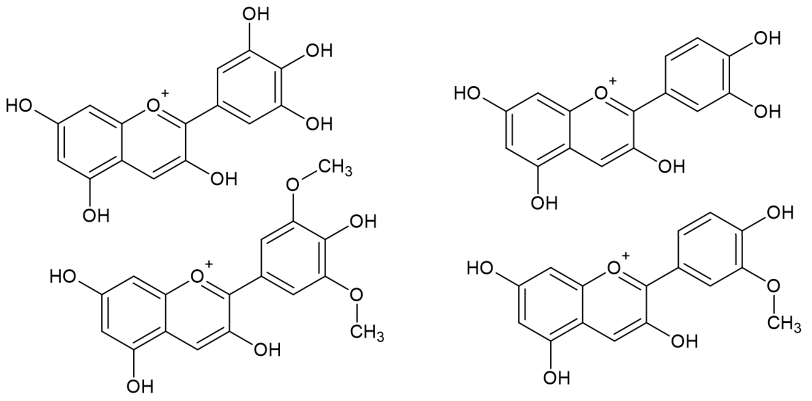


In the picture you can see a strong similarity between endocannabinoids and THC. Substances that resemble endogenous neurotransmitters and therefore exhibit similar activity are called mimetics or agonists.

There are many subtle mutual correspondences in such structures, for example, the carbon involved in the simple ether cyclic bond in THC is electronegative and has no hydrogens, which makes it related to the ketone carbon of arachidic acid. In the CBD molecule, there is a methylene double bond on the tertiary carbon, which also functions as a pro-ketone radical.

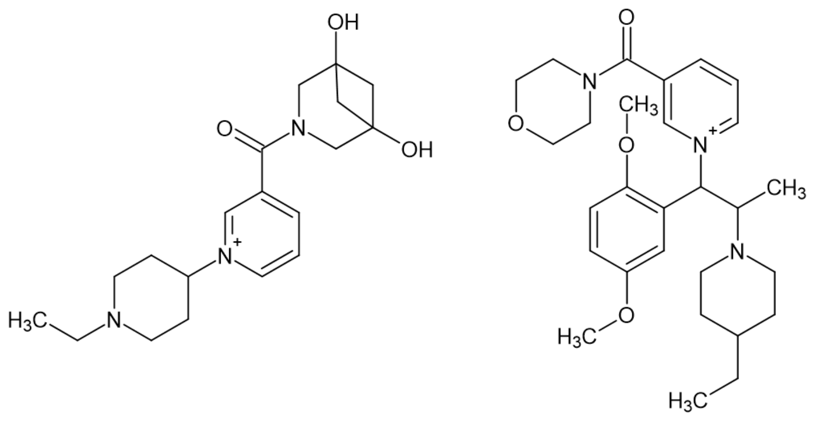
As a rule, simple mimetics are much less active than natural hormones and neurotransmitters, but they have an undeniable advantage, they are much more stable inside the body, they can act for a long time, they can pass biobarriers and the encephalic barrier, but our goal is to regulate these indicators and create structures with unique properties.

A cannabinoid can easily be transformed from a lipophilic agent into a hydrophilic polar agent, as well as into a bulky object that does not pass the blood-brain barrier. Anthocyanins are natural dyes that are also often anti-cancer in nature, and are bulky and polar structures, the property to paint tissues for a long time can be useful for external use and for the treatment of gastrointestinal oncology:

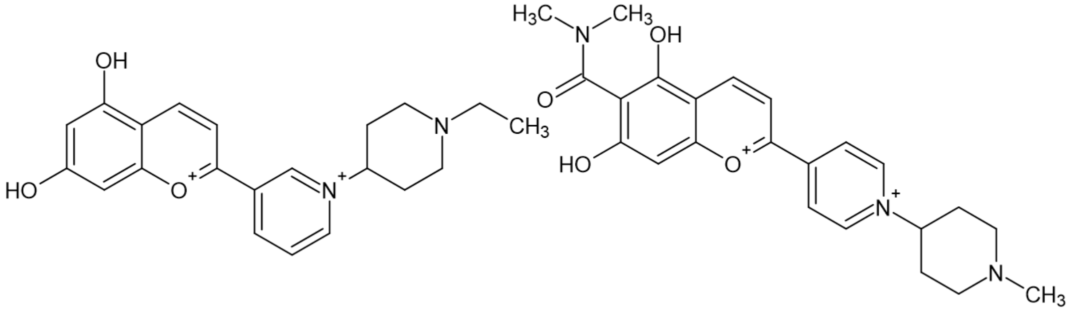


Anthocyanins - promising nuclei for the creation of anti-cancer non-narcotic cannabinoids.

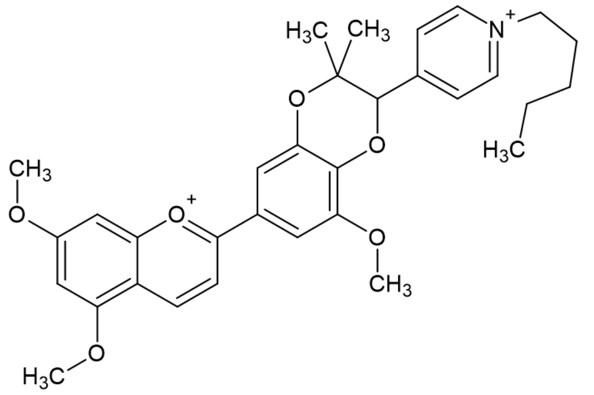
From simple to complex.

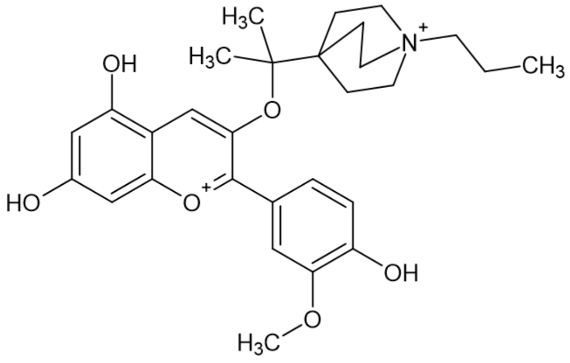


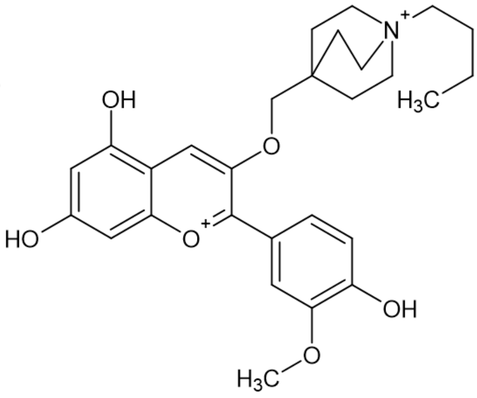
Pro-Cannabinoid quaternary ammonium bases and hydrophilic amines.



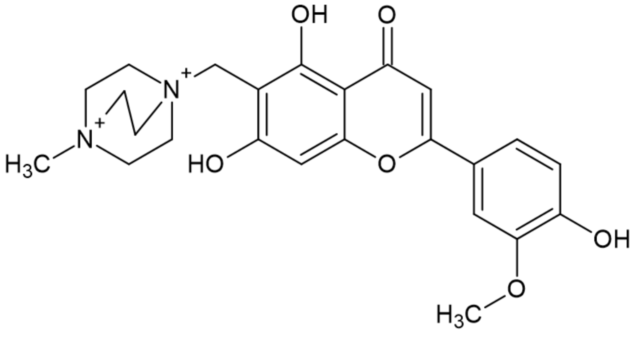
Synthetic analogues of anthocyanins.

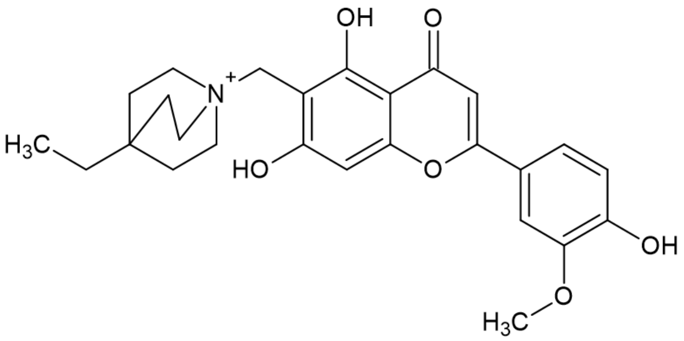






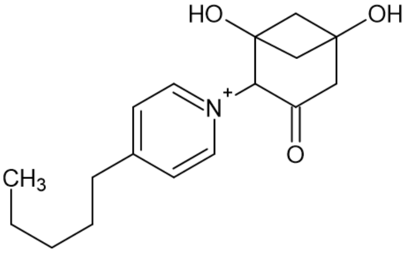
Pro-Cannabinoid derivatives of anthocyanins.

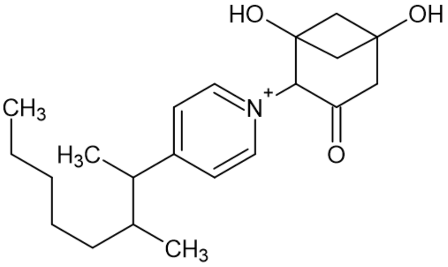




Substances close to anthocyanins - flavones, are more lipophilic, but are much more easily converted into a pro-cannabinoid core, and may also be very promising for obtaining high-affinity peripheral anti-cancer cannabinoids. Such substances can act inside the esophagus, in large doses, almost without getting into the blood.

Less complex quaternary ammonium bases have a more compact structure, dissolve well in water, are convenient for oral administration, as well as for intravenous administration, inhalation administration and external use. Such structures can also have special physicochemical properties. For example, these can be structures with surface-active properties - molecules with a linear lipophilic tail and a powerful hydrophilic radical at the beginning of the molecule:

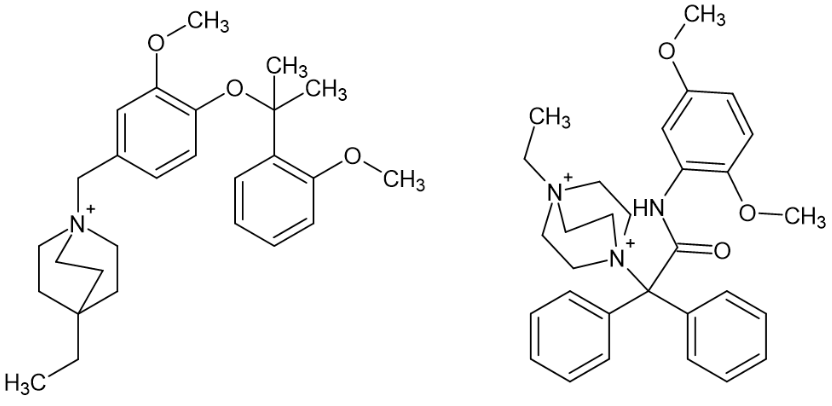




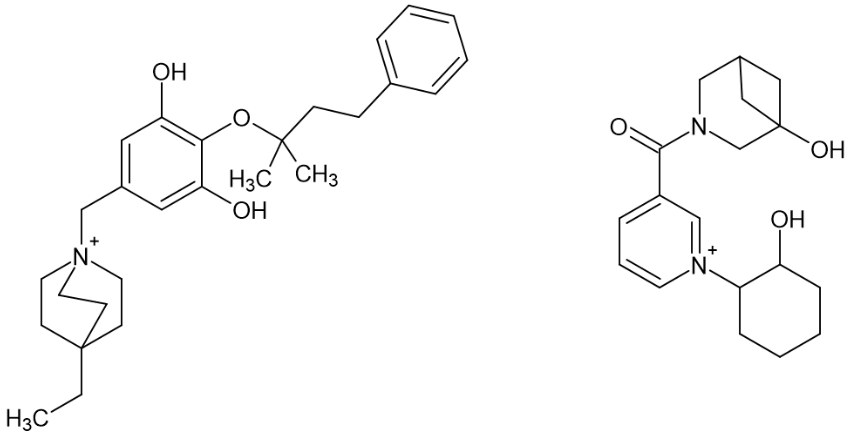
Surfactants can accumulate or be retained in some organs. For example, in the lungs, since the lungs have a large contact surface between two phases, where both surfactants can accumulate and quaternary ammonium bases, which poorly overcome biomembranes, can be sorbed.

Various delivery methods, such as inhalation, injections directly into metastases, application to the skin, intravenous injections, can provide a prolonged point effect or a general powerful effect, depending on the delivery method and the physicochemical properties of the drugs.

If a substance has specific radicals that interfere with penetration through biomembranes, when injected into cancer tissue foci, the drug will have a therapeutic effect at the injection site for a long time. If such a drug is applied to the skin or inhaled, such a drug will function for a long time at the sites of application and absorption. If the substance penetrates biomembranes sufficiently (some quaternary ammonium salts), then an intravenous injection can give a powerful signal to the entire body in a few minutes, causing a powerful peripheral anti-cancer immune response.



Example of linear and globular structure.



An example of a substance with high and low affinity.

When developing a strategy for the design of drugs, many criteria must be taken into account, and the more rational data is put into the structure of the drug, the less test structures will need to be synthesized for testing and selection, this is the essence of a rational approach to drug design, to give a theoretical start to new drugs and minimize costs during development.

Every substance entering the body must be non-toxic in active doses, non-carcinogenic, non-mutagenic, non-hepatotoxic.. It must be excreted from the body unchanged, or in the form of safe catabolites. These are hundreds and hundreds of criteria, because we are talking about a substance as a sum of radicals and properties.

To understand some patterns, I spent years analyzing various drugs, synthesizing and testing some derivatives. Pharmacology is too big a discipline for one person to be engaged in rational drug design in hundreds of areas. For this reason pharmacology is not an exact science, there are always many surprises along the way, it is always a minefield, crossing which is a real art.

Simple rules allow you to avoid gross design errors:
Do not use unstable compounds and radicals. And then you will not get a mutagen or an unstable compound that will have to be protected from the body's enzymes with halogenated aromatic nuclei. Do not use toxic nuclei. Do not use cytochrome-inhibiting fragments, such as a keto group located close to a double bond. Do not use biolabile aromatic nuclei. Build radicals in such a way that the structure loses activity first, and acquires potentially unnecessary properties after complete loss of activity. That is, include catabolic pathways in the design of substances. In the case of centrally active substances, the requirements are significantly increased, it is necessary to take into account the danger of lipophilic catabolites, residual activity, the ability to accumulate and change activity. A balance of radicals is required, radicals must have a commensurate strength of complementary interaction. It is necessary to control the structures for selectivity, small molecules can often affect several targets, this property is better used as a tool, rather than as a source of side effects of the drug being developed.

# Rational design cannabinoids, based on quaternary ammonium bases that do not cross the blood-brain barrier.

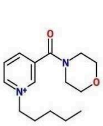
Taking with quaternary ammonium bases has several advantages in the development of cannabinoids. Firstly, such substances do not pass the blood-brain barrier and do not have a narcotic effect, which is critically important for ease of use and mass use. Secondly, both CB2 and CB1 active substances have anticancer properties, as well as GPR-55 in some cases. It is obvious that selective drugs may be less versatile and possibly less active, and complex quaternary ammonium bases may be the most convenient and effective solution for the pharmacological market.

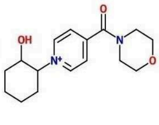
It is also worth noting that quaternary ammonium bases may have anticancer potential as ion blockers on the surface of biological membranes. They can also be active as apoptosis inducing agents, with anticancer radicals close to terpenes and phenols, this can enhance the anticancer effect.

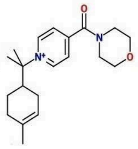
Also, a feature of the presented design is a wide range of physicochemical and pharmacological properties: Surface active properties - such substances can accumulate in the lungs when administered by inhalation. Also, substances can accumulate in the gastrointestinal tract, because such substances do not pass biological membranes relatively quickly. It is an excellent prospect for use in cases of skin, gastrointestinal or lung cancer. Also, these substances are well soluble in water and can be used by injection, intravenous .. including injections into the focus and metastases.

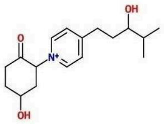
Separately, it is worth noting the fact that this design blocks any attempts to synthesize narcodrugs from quaternary bases (as is the case with methylnaltrexone). When dealkylation of substances of this design, inactive derivatives are formed, which completely excludes even the minimal possibility of using substances as starting materials for obtaining narco drugs on the black market. Thus, the issue of narco drugs is removed from the agenda, and drugs can probably be dispensed without a prescription.

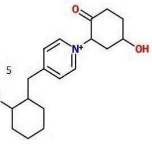
Examples of structures:

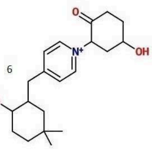
1


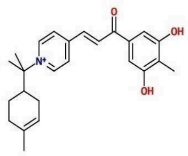
2


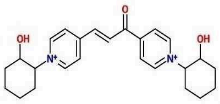
3


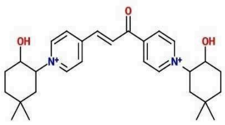
4


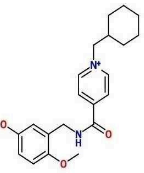
5


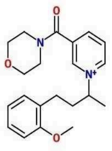
6


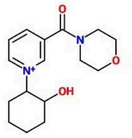
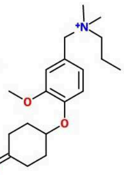
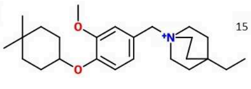
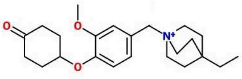
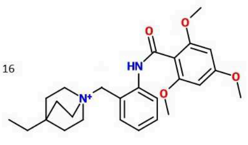
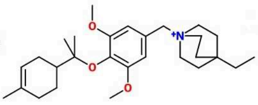
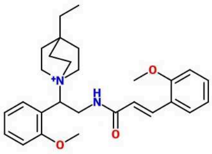
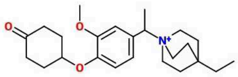
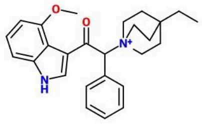
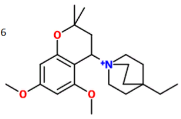
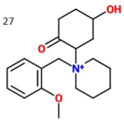
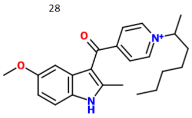
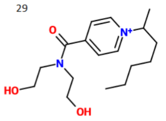
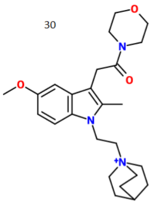
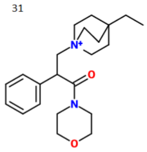
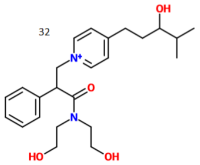
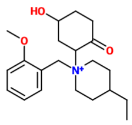
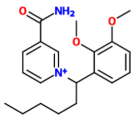
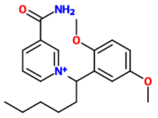
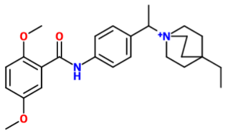
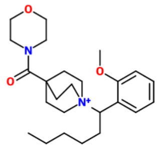
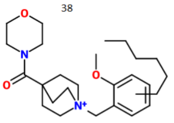
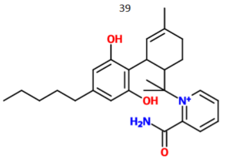
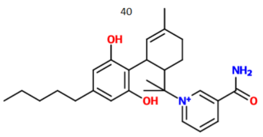
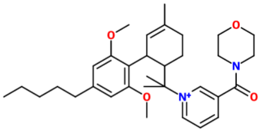
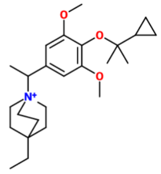
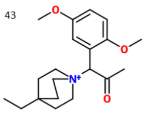
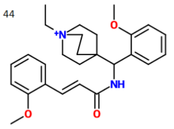
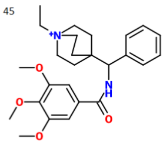
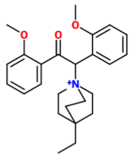
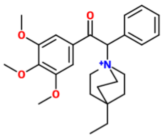
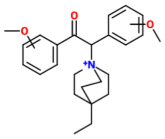
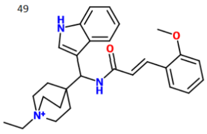
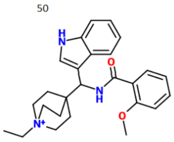
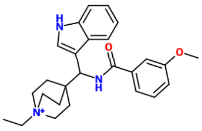
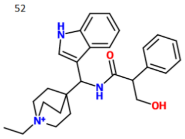
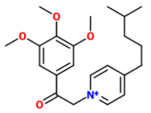
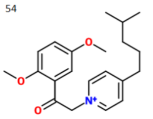
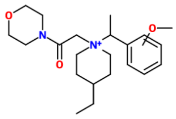
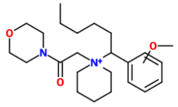
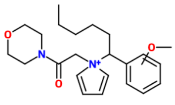
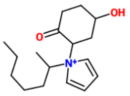
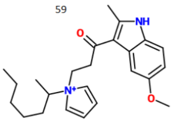
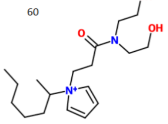
7


8


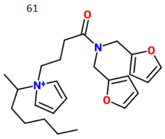
9


10


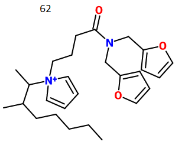
11


12

13

14

15

16

17

18

19

20

26

27

28

29

30

31

32

33

34

35

36

37

38

39

40

41

42

43

44

45

46

47

48

49

50

51

52

53

54

55

56

57

58

59

60


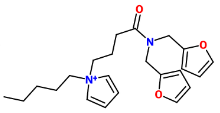
61



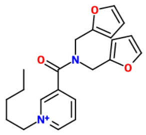
62



63

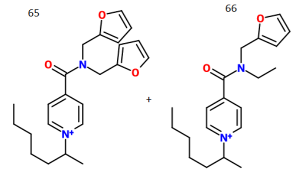


64

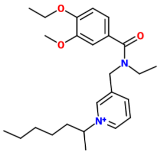


65

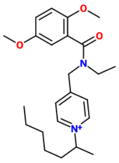
66



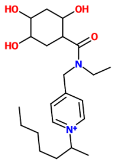
67



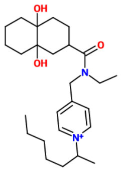
68



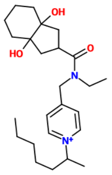
69



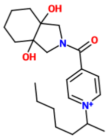
70



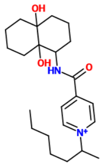
71



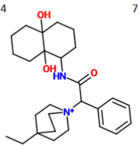
72



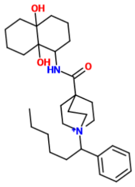
73



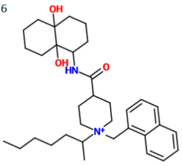
74



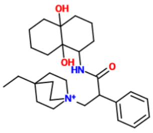
75



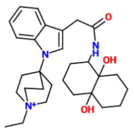
76



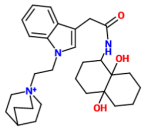
77



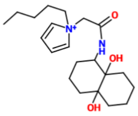
78



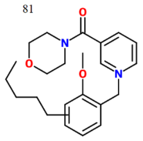
79



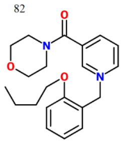
80



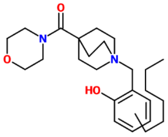
81



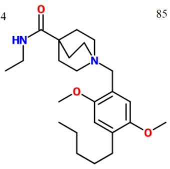
82



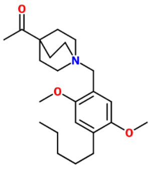
83



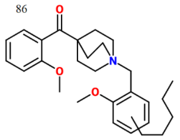
84



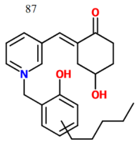
85



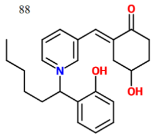
86



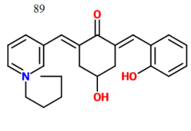
87



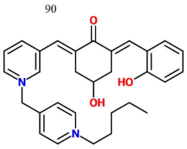
88



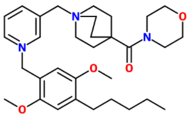
89



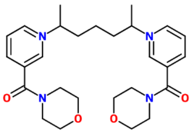
90



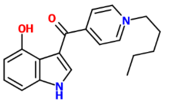
91



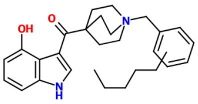
92



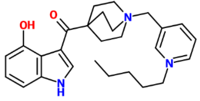
93



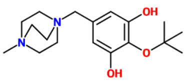
94



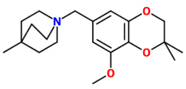
95



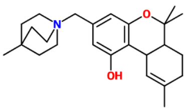
96



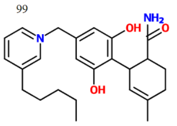
97



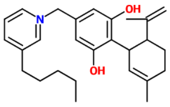
98



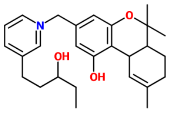
99



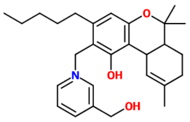
100



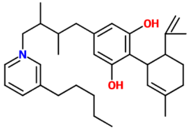
101



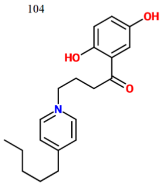
102



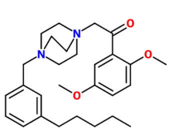
103



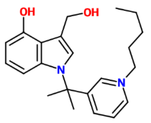
104



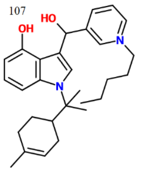
105



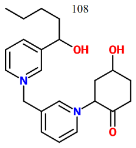
106



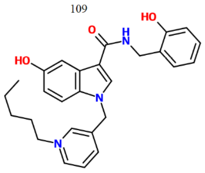
107



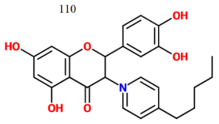
108



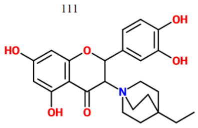
109



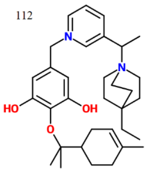
110



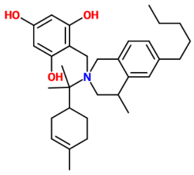
111



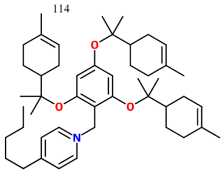
112



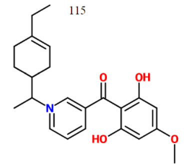
113



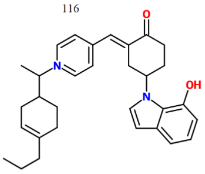
114



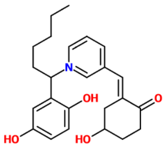
115



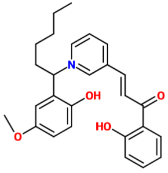
116



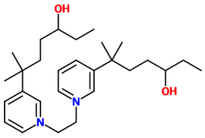
117



118



119



The above diversity of kernels, isomers and design options aims to expand the range of synthetic and semi-synthetic cannabinoids for a more productive search for convenient and effective anti-cancer agents.

The presence of an amine nitrogen atom in the structure, subject to certain rules, does not affect the affinity. Although there are not very many natural and synthetic cannabinoids in the world, among the known cannabinoids there is a wide variety of forms, from kava lactones to caryophyllene, from cannabidiol to WIN55212.

Thus, this work can serve as an impetus for the discovery of new properties of cannabinoids, the development of necessary pharmacological drugs, such rare groups as local and peripheral activators of anticancer immunity. Moreover, the list may also include drugs capable of exerting a therapeutic effect on oncological tumors of the brain, since immune cells are partially able to penetrate the blood-brain barrier.

# Peripherally Selective bioavailable Cannabinoid Receptor Type1. (CB1) Antagonists and (CB2) Agonists. Rational Design.

Selective antagonists of cannabinoid CB1 receptors are promising as metabolism correctors, anticancer agents, immune correctors in autoimmune disorders, and much more.

The main limiting qualities of currently existing antagonists of cannabinoid receptors type 1 are central activity, poor bioavailability, and side effects of individual representatives of such structures.

Rational drug design in the case of antagonists of cannabinoid receptors type 1, comes down to obtaining, if possible, compact small molecules, bioavailable, biostable, highly active, while not passing the blood-brain barrier, but partially passing biomembranes.

The last point can vary depending on the route of administration and the selected target. For example, in the case of introduction into an organ or a site of cancer tissue growth, such as the lungs, by inhalation, drugs with minimal ability to pass through biomembranes can be used to accumulate the drug in the lungs and for long-term application.

Accordingly, rational design should be based on radicals that implement a wide range of the above-described physicochemical properties. As well as nuclei composed of similar radicals that implement the pharmacological scheme of the antagonist.

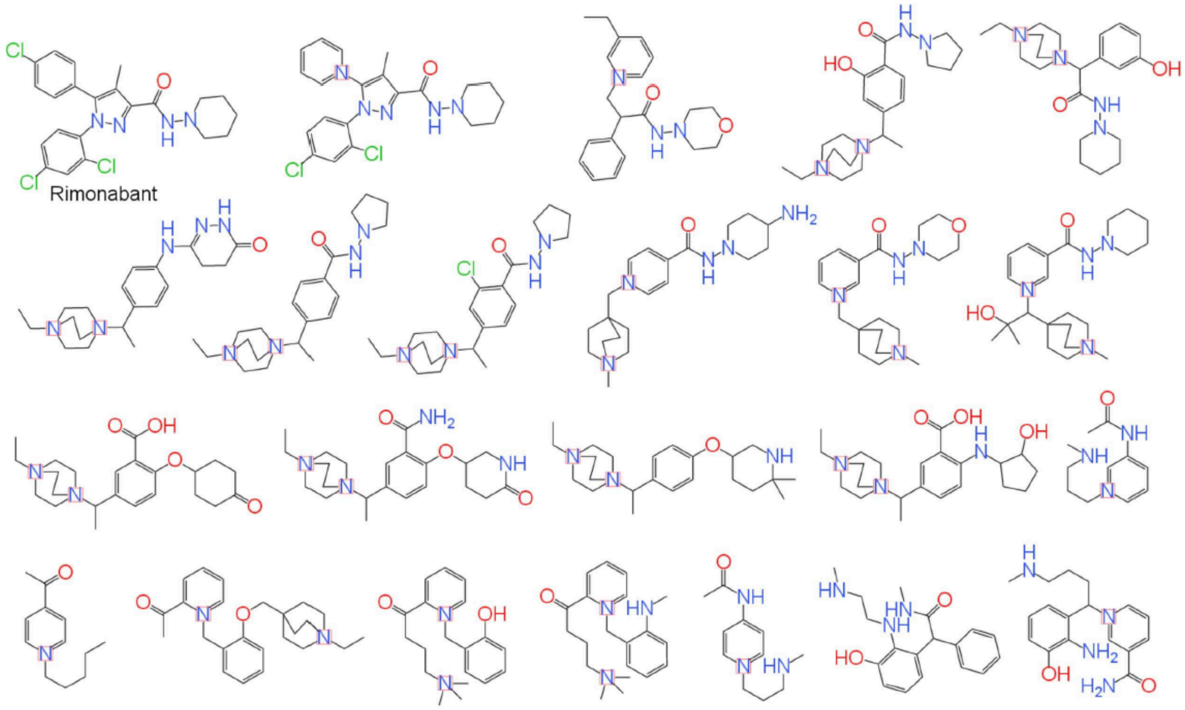
To develop such structures, many combinations of radicals and special nuclei of chemical structures were selected that could potentially have the above characteristics. The structures were not built on the basis of a single nucleus; they have a large difference in structure and mechanisms of action.
Particular attention was also paid to the potential affinity of the proposed structures, because this indicator is extremely important in oncological applications.

The pharmacology of this group of drugs is based on several pharmacological variations of the implementation of the antagonistic action.

Multiplying the number of pharmacological solutions and their implementation options by the number of solutions regarding pharmacological synthesis. Also the expected catabolism of substances, expected activity, selectivity, ability to penetrate through biomembranes, bioavailability and ability not to penetrate through the blood-brain barrier.

A significant number of variations are formed, some of which are presented in this work. It is also worth noting that although the list is extensive and the substances presented are quite typical, it is possible to significantly expand such a list, since these examples are only particular examples of the selected design strategies and tactics.

Examples of structures:



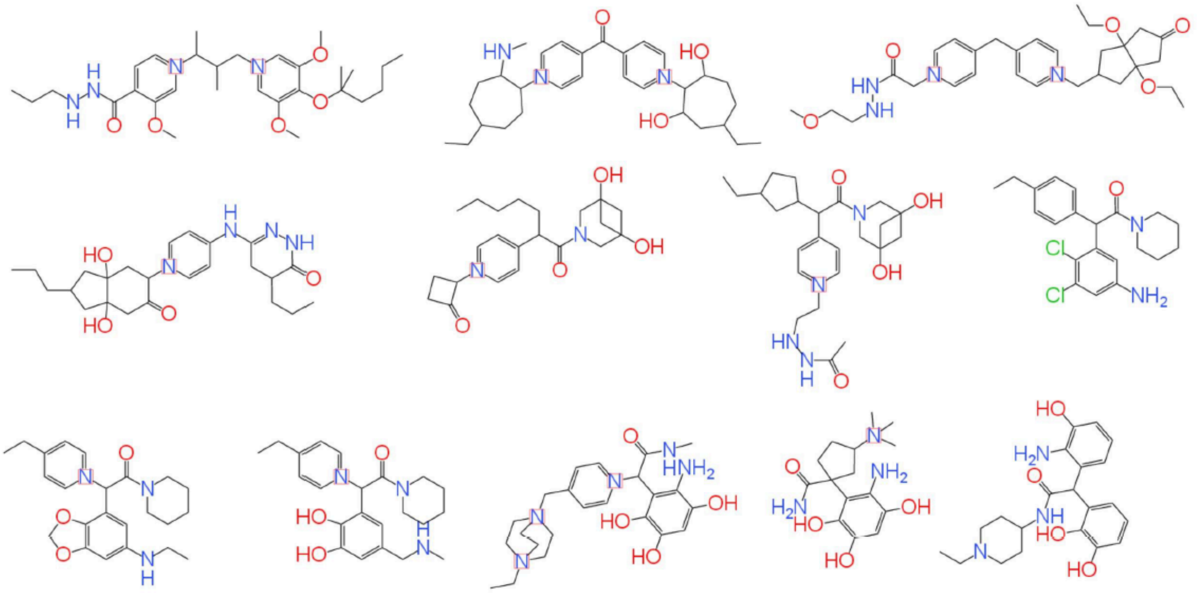
Since the anticancer properties of cannabinoid receptor type 1 antagonists in pharmacological practice can be associated with other cannabinoids, such as cannabinoid type 2 agonists, there is a demand for universal antagonist-agonists.

The implementation of the antagonist-agonist design in pharmacology is possible through various rational tactics. But this case is unique and requires a completely new implementation path. Since the task is to implement an agonist of CB2 (and/or GPR55) receptors and a selective antagonist of CB1 cannabinoid receptors in one structure, the proposed structures must have unique and expanded capabilities.

As a basis for distinguishing such seemingly mutually exclusive functions, the dual activity of isomers, tautomers, duplicated radicals and condensed structures was chosen. The complexity of pharmacology and the expected kinetics of molecules should not affect quality indicators such as bioavailability, molecular weight, availability of pharmacological organic synthesis.
To achieve this goal, it is necessary to qualitatively combine and qualitatively separate the corresponding radicals, avoiding excess molecular weight and other side-effects.

Nevertheless, the construction of such drugs is extremely attractive, because they allow you to use one drug instead of several, and also, which is important, the development of such a drug can be literally twice as affordable as several drugs. After all, preclinical and clinical trials of new drugs make up a significant part of the cost of searching for and developing drugs. Also, in the case of a successful design of such a drug, precious time is saved.

Design examples:



While obtaining complex agonists-antagonists has theoretical prerequisites for implementation, more complex drugs that include more than two cannabinoid receptor responses are a more unattainable goal. Inclusion of GPR55 agonists is possible, moreover, fundamentally necessary, but at this stage it is more appropriate after obtaining the first data on the activity of the above-listed structures.

At the same time, having experience in the design of anti-cancer cannabinoids of various groups, physicochemical and pharmacological properties, it is possible to significantly optimize the current search and development of drugs.

# New pharmacological cores of GPR55 Receptor Antagonists and Agonists. Rational Drug Design, small molecules.

Antagonists of GPR55 receptors are promising as anti-inflammatory, immunomodulatory and anticancer agents. The pharmacological design of drugs of this group has a number of characteristic features, such as a close relationship with the structures of cannabinoids of other groups, many strategies for implementing the functions of an agonist and antagonist, difficulties in obtaining high selectivity and special useful combinations of non-selective activity.

Antagonists of GPR55 receptors are perfectly combined with agonists of CB2 receptors, since their pharmacological profiles complement each other, and the structures of endogenous cannabinoids with affinity to GPR55 and CB2 are similar in chemical structure, as are their natural and synthetic agonists. The latter allows implementing the strategy of designing complex agonists and agonist-antagonists to obtain drugs with a wide range of therapeutic effects and synergy.

The main tasks for rational drug design in this work were, development of strategies of antagonists and agonists of GPR55 receptors with a unique pharmacological profile, providing pure and simple organic synthesis, absence of toxic and radical inclusions in the structure, timely and safe catabolism, high bioavailability, moderate biostability. And also a range of special physicochemical and pharmacological properties, such as high or low affinity, high or low activity, ability to pass or not pass the blood-brain barrier, ability to linger at the injection sites, internal organs, on the surface of the skin or lungs, ability to be carried by the blood stream upon injection...

All of the above parameters are necessary for the implementation of drugs with different qualities, to achieve high results in the treatment of various pathologies requiring different methods of administration, external or inhalation, subcutaneous or intravenous, central or peripheral.

Also, the development of strategies for complex antagonist-agonists, GPR55 antagonists and CB2 receptor agonists in one structure, as well as GPR55 agonists, which are also being studied for their beneficial properties, requires rather subtle strategies for constructing rational design, which was demonstrated in this work.

The design of such structures is associated with difficulties in obtaining bioavailable structures, which is due to their bulky structure, often due to a large number of heteroatoms with radicals in the form of halogenated aromatic groups. With a decrease in the molecular weight of such structures, biostability often decreases, which sometimes forces one to balance on the edge of possibilities. Such a powerful pharmacological technique as combinatorial heterochemistry cannot always be an answer to any challenge, especially when it comes to mimetics or antagonists of substances that have almost no heteroatoms.

On the other hand, the old school of drug design is often associated with homologues and derivatives of natural cannabinoids, the synthesis of which is difficult and inaccessible, especially in the case of mass synthesis of candidates for the role of a pharmacological drug.

Deadlock and compromises, is there a way out? A useful find in this direction can be a deep rational design including elements of combinatorial chemistry based on fine organic synthesis as an elementary brick of combinatorial synthesis. In this way, the structure will not be bloated by heteroatoms and pharmacology will receive a simple, clean, high-quality mechanism for the synthesis.

What does deep rational drug design mean? It means the application of modern knowledge to the construction of pharmacological methods and design methods without or together with computer modeling, but necessarily an intelligent approach for deep analysis of the material. For example, statements that computer modeling has an advantage in that it is able to obtain the most highly affinity drugs are not true, because even in the pre-computer era, drugs with maximum affinity were created by analyzing data and deep design based on rational drug design.

For example, the design of GPR55 antagonists based on CBD derivatives involves complex synthesis, which complicates testing a large number of such molecules. It is possible to remove the limiting factor, for this it is necessary to understand the pharmacological scheme of CBD activity, apply this and a number of similar schemes and pharmacological maneuvers to build more accessible pharmacological analogs based on simple initial and simple reactions, pure reactions, inexpensive precursors, with simple methods for obtaining derivatives, within the framework specified above.

The requirements and frameworks are extensive and comprehensive, but there are also many opportunities for implementation. In the course of writing this work, dozens of cores and hundreds of structures were developed that implement various strategies for obtaining agonists and antagonists, complex agonists-antagonists, drugs with special properties, for example, not passing the blood-brain barrier. Also shown in the illustration are substances of different lipophilicity, ability to pass through biomembranes and other properties.

The purpose of such a wide range of forms, qualities and possibilities was the maximum approximation to the required qualities for various groups of drugs - anticancer drugs, drugs to combat autoimmune reactions, for central and purely peripheral drugs, for obtaining water-soluble and water-insoluble drugs, for obtaining drugs that do not leave the organ into which they were introduced, or for obtaining drugs that are well distributed and maximally bioavailable, but do not pass the blood-brain barrier or pass it.

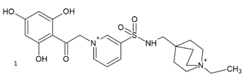
Such pharmacological and physicochemical properties are required for the development of special forms of anticancer drugs, central or peripheral drugs, and, importantly, some properties, such as the inability to penetrate the blood-brain barrier, are extremely useful in the development of non-narcotic drugs that do not give central side effects, which improves their safety and opens up wide opportunities in the market.

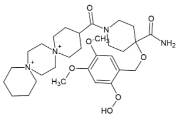
In this work, dozens of strategies for obtaining agonists and antagonists, as well as complex agonists-antagonists of GPR55 and CB2 related structures, were implemented.

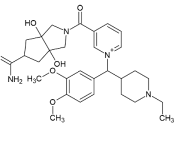
But, nevertheless, the structures remain unlabeled, because to confirm the activity, it is necessary to carry out synthesis and activity studies. This work is only an example of strategies and tactical maneuvers of deep rational design, since there is a chance of error when the supposed agonist will show antagonist activity and vice versa, the supposed antagonist will turn out to be an agonist, the structures are not described, especially since too many expositions were required to describe each structure.

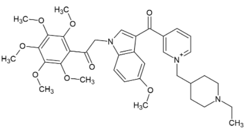
The main messages will be the simplicity of combinatorial chemistry of fine organic structures, implementation of various strategies for constructing agonists and antagonists, deep work on discovering new pharmacological maneuvers in the design of structures, design of an extended spectrum of physicochemical and pharmacological properties. Preliminary edits of toxicity, catabolism, biostability and biolability, bioavailability, penetration of special barriers, saturation and unsaturation of structures, high affinity and activity, ease of synthesis and availability of precursors, purity of reactions (pharmacological organic synthesis), control and spectrum of molecular weight, lipophilicity, compactness of the solution of a pharmacological problem, static and dynamic behavior, change of configurations...

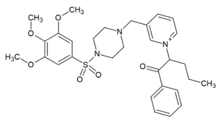
Examples of structures:

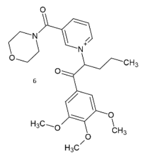
1


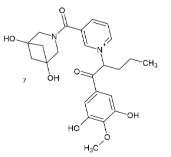
2


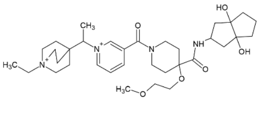
3


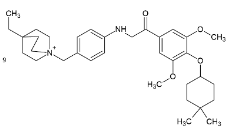
4


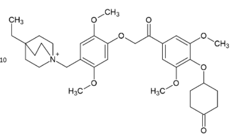
5


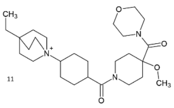
6


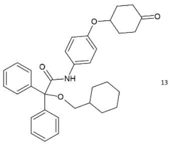
7


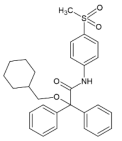
8


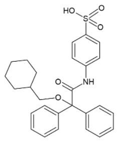
9


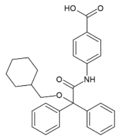
10


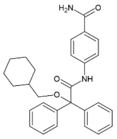
11


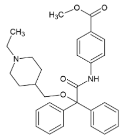
12


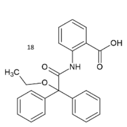
13


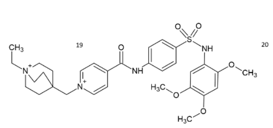
14


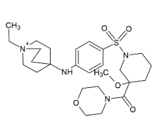
15


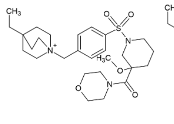
16


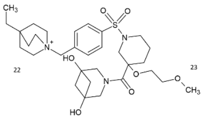
17


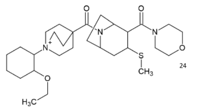
18


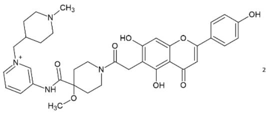
19


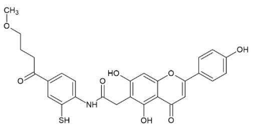
20


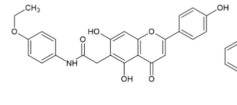
21


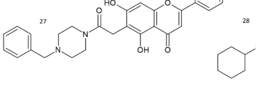
22


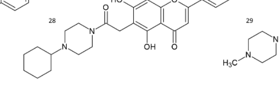
23


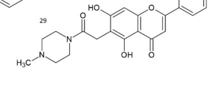
24


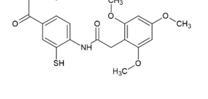
25


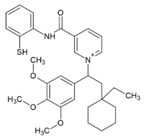
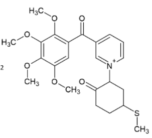
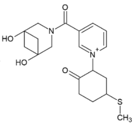
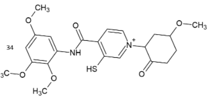
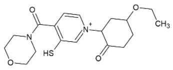
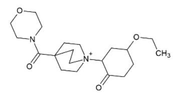
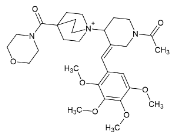
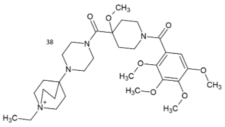
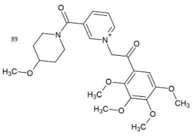
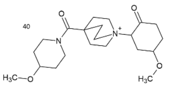
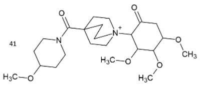
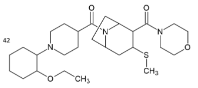
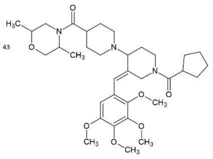
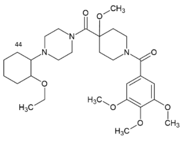
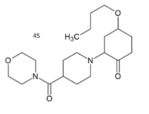
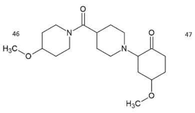
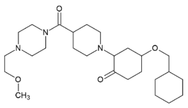
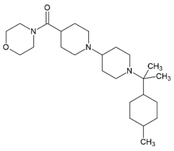
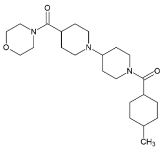
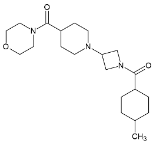
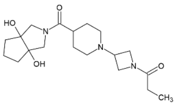
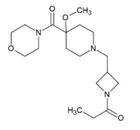
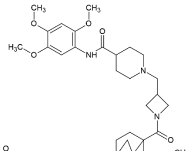
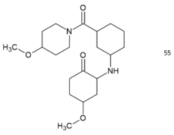
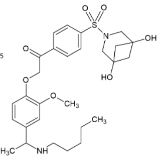
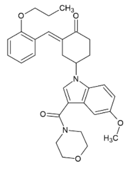
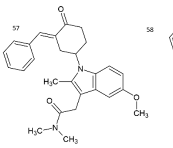
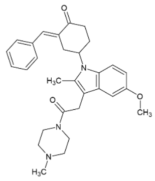
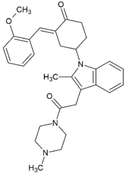
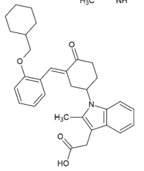
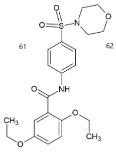
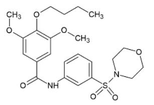
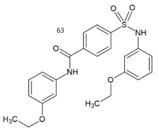
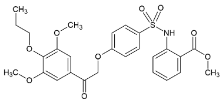
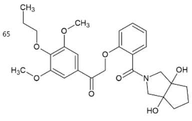
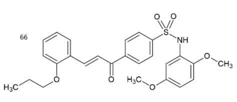
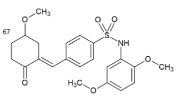
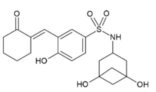
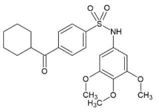
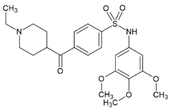
26


27


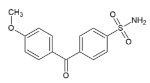
28


29


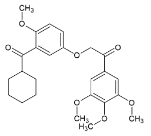
30


31

32

33

34

35

36

37

38

39

40

41

42

43

44

45

46

47

48

49

50

51

52

53

54

55

56

57

58

59

60

61

62

63

64

65

66

67

68

69

70


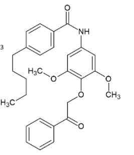
71



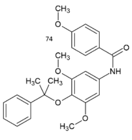
72



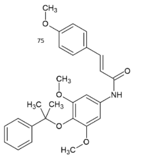
73



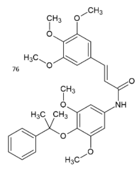
74



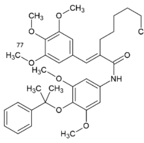
75



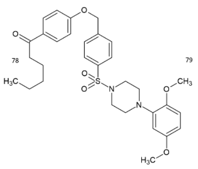
76



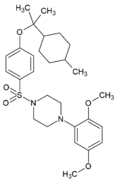
77



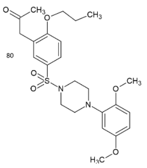
78



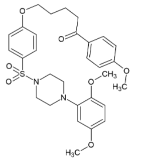
79



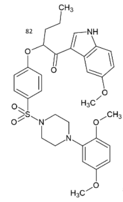
80



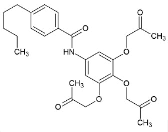
81



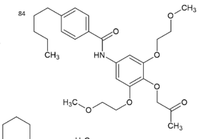
82



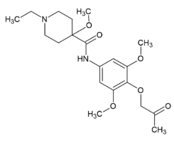
83



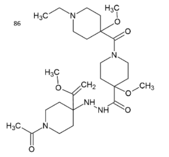
84



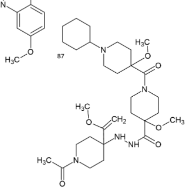
85



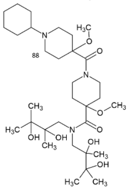
86



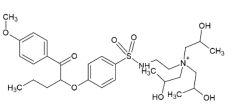
87



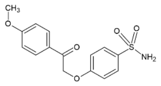
88



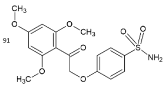
89



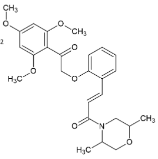
90



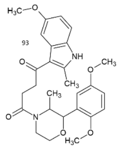
91



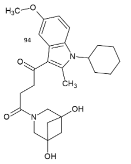
92



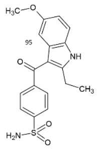
93



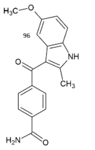
94



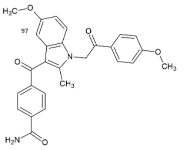
95



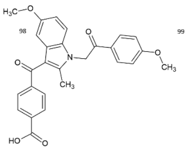
96



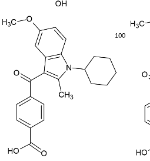
97



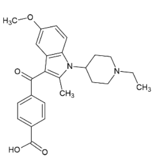
98



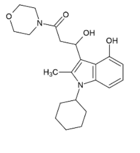
99



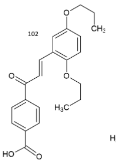
100



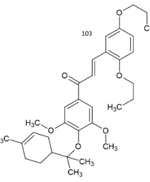
101



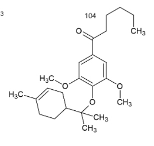
102



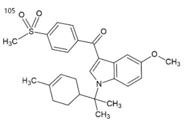
103



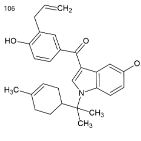
104



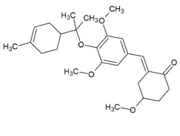
105



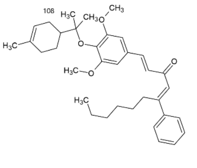
106



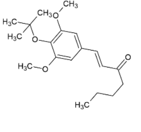
107



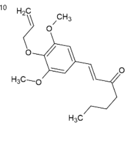
108

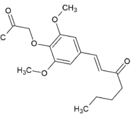
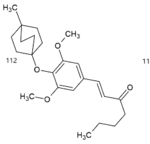
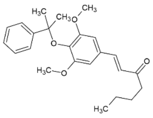
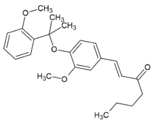
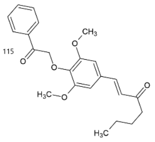


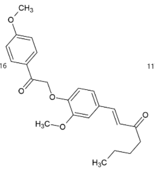
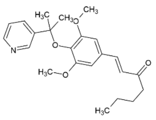
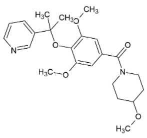
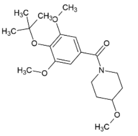
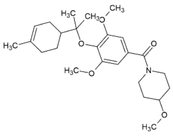
109

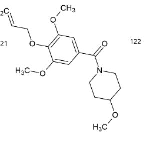
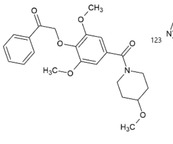
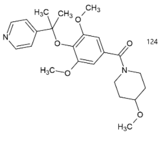
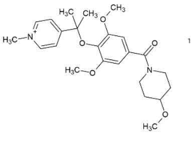
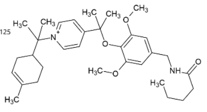


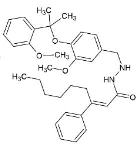
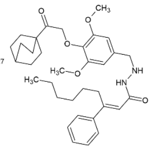
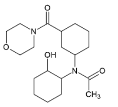
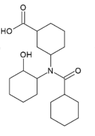
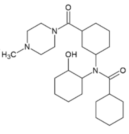
110

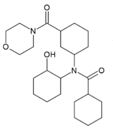
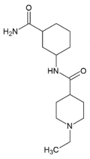
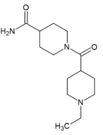
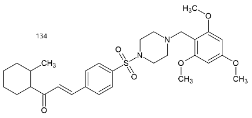
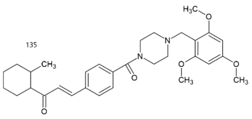


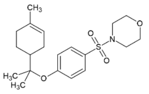
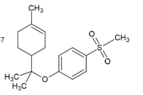
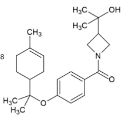
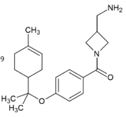
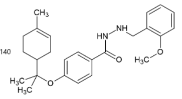
111

112

113

114

115


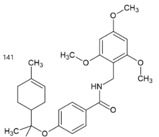
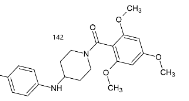
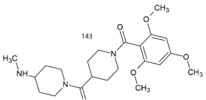
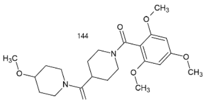
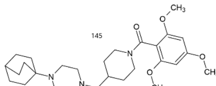
116

117

118

119

120


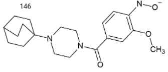
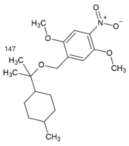
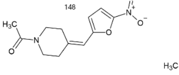
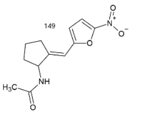
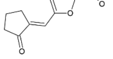
121

122

123

124

125


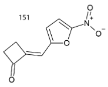
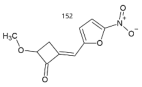
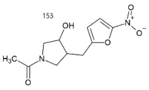
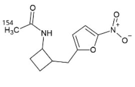
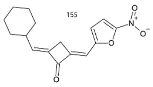
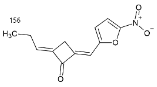
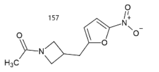
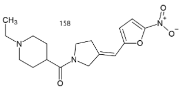
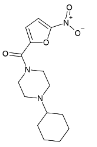
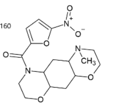
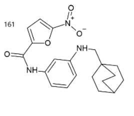
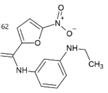
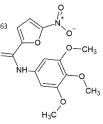
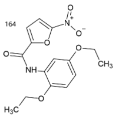
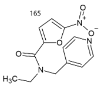
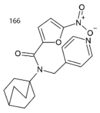
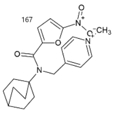
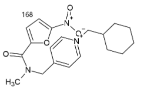
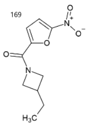
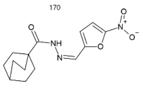
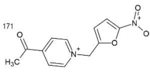
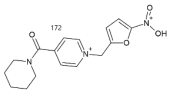
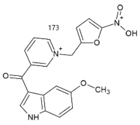
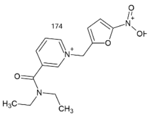
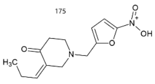
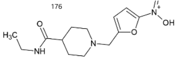
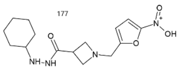
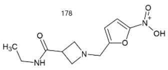
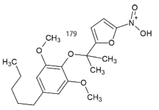
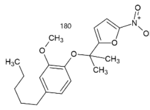
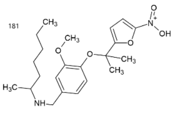
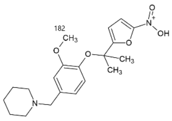
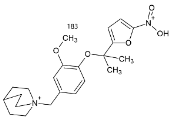
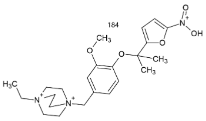
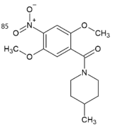
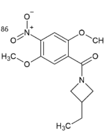
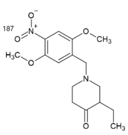
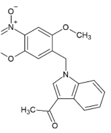
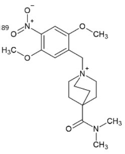
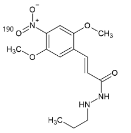
126

127

128

129

130


131

132

133

134

135


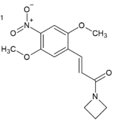
136

137

138

139

140


141

142

143

144

145


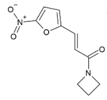
146

147

148

149

150


151

152

153

154

155

156

157

158

159

160

161

162

163

164

165

166

167

168

169

170

171

172

173

174

175

176

177

178

179

180

181

182

183

184

185

186

187

188

189

190


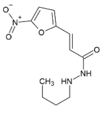
191



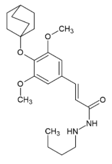
192



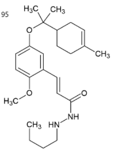
193



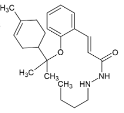
194



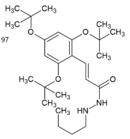
195



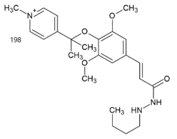
196



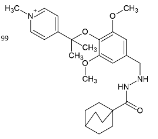
197



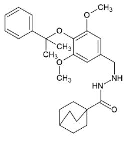
198



199



200



The structures presented above implement both existing and completely new pharmacological strategies for obtaining GPR55 agonists and antagonists of cannabinoids. The depth of rational design allowed us to abandon the complex structures of natural cannabinoids, as well as cumbersome hetero chemical structures, and implement combinatorial chemistry based on fine synthetic substances, while reducing the number of candidates through deep rational work.

The mechanisms of activity of agonists and antagonists of GPR55 receptors have not been fully studied. The effects of such cannabinoids are diverse and will probably require careful selection of therapeutic methods in the future. Also, in addition to the standard agonistic or antagonistic action, alternating innervation and blinding of the receptor is possible. For example, for a powerful immune response to a sharp change in the tone of the cannabinoid system, to reduce tolerance and other effects. Or to achieve a special therapeutic effect, in the event that neither agonists or antagonists separately give the desired result. GPR55 agonists and antagonists have the potential for multifaceted use. They can probably complement the anticancer and anti-inflammatory effects of CB2 agonists and CB1 antagonists.

Since it is theoretically possible to create complex agonists/antagonists, it is worth considering the ability of the structure to act on several targets simultaneously in the desired manner. Such substances can reduce development costs several times and be much more convenient to use.

# CBD, highly active, pharmacological derivatives.

CBD derivatives are extremely rarely used to search for potential anti-cancer drugs.., giving preference to synthetic, often poly-hetero chemical compounds.

This is easy to explain, given the complexity and cost of synthesizing the simplest CBD derivatives, the inconvenience of working with terpenes and, perhaps most importantly, an insufficiently close look at the problems of drug design and pharmacological synthesis of terpenes.

This work demonstrates the hidden potential of terpenes in pharmacology, organic pharmacological synthesis, biotechnological synthesis and drug design. Sooner or later, the use of terpenes, both natural and semi-synthetic and synthetic, will be realized, because poly-hetero chemical cannabinoids are initially a controversial decision, given the fact that they are mimetics of amides and esters of fatty acids, substances that are extremely far from hetero-chemical nuclei structurally and functionally.

Upon closer examination of the structure of CBD, CBDA, and possible biotechnological derivatives such as CBDPA, it is impossible not to notice the many variations of derivatives suitable for the search for highly active and effective analogues of CBD.

The carboxyl group in the CBDA and the phenyl group of THC and CBD structure allows for the production of substances with an additional amide group, aromatic core, with additional hydroxyl radicals and their combination, which can greatly enhance the maximum efficiency and activity of CBD without interfering with selectivity relative to CB-2 receptors.

And using the simplest methods of biotechnological synthesis, for example, by adding an acid with an extended chain to marijuana tissues that produces CBDA, it is possible to obtain a derivative of CBDP - a substance with a potential increase of probably more than tenfold, CBDPA is a simple starting material for the simple synthesis of highly active derivatives of CBD.

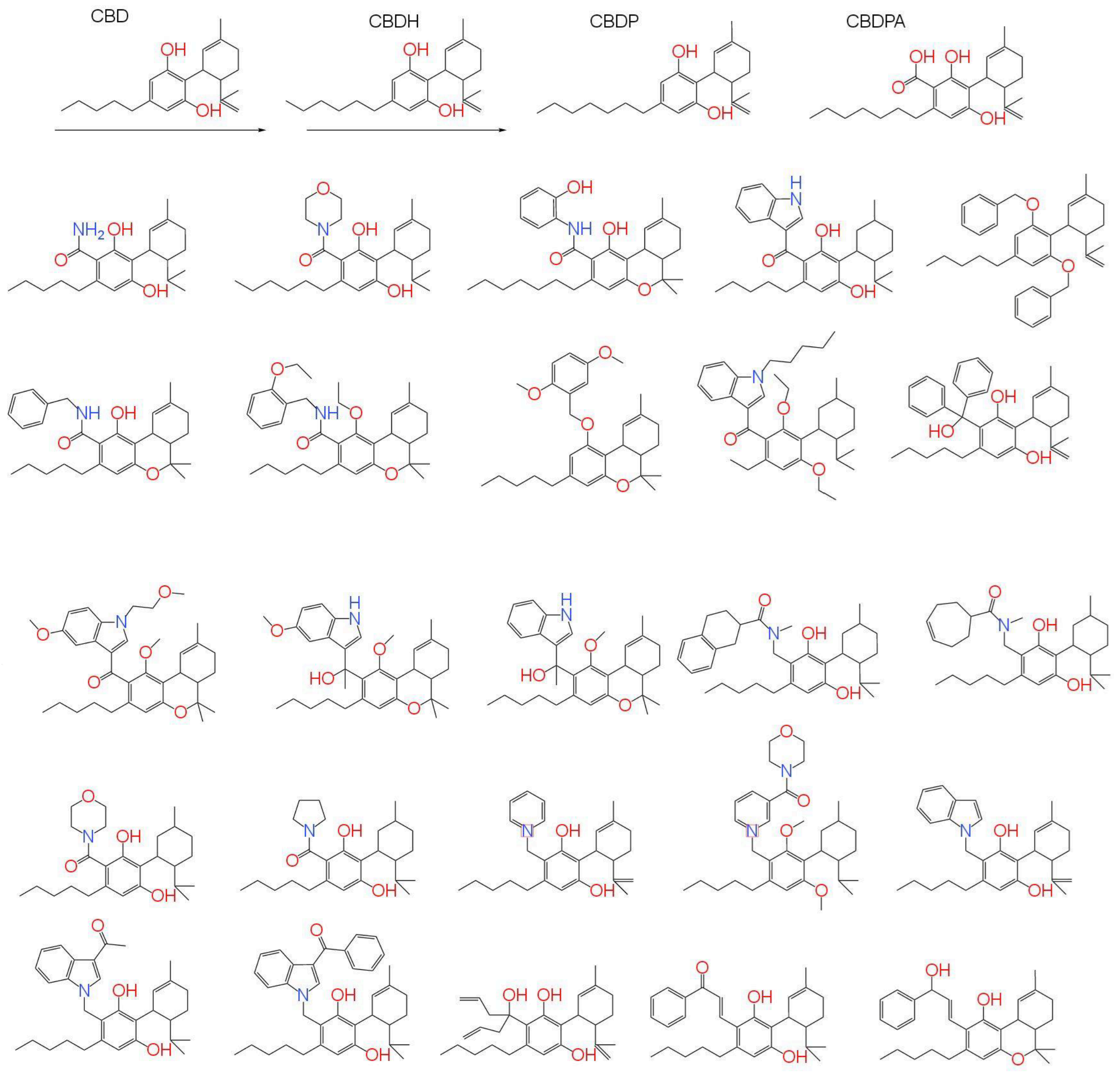
In both cases, highly active derivatives can exhibit activity starting from tens of micrograms, which can make this method even more cost-effective.

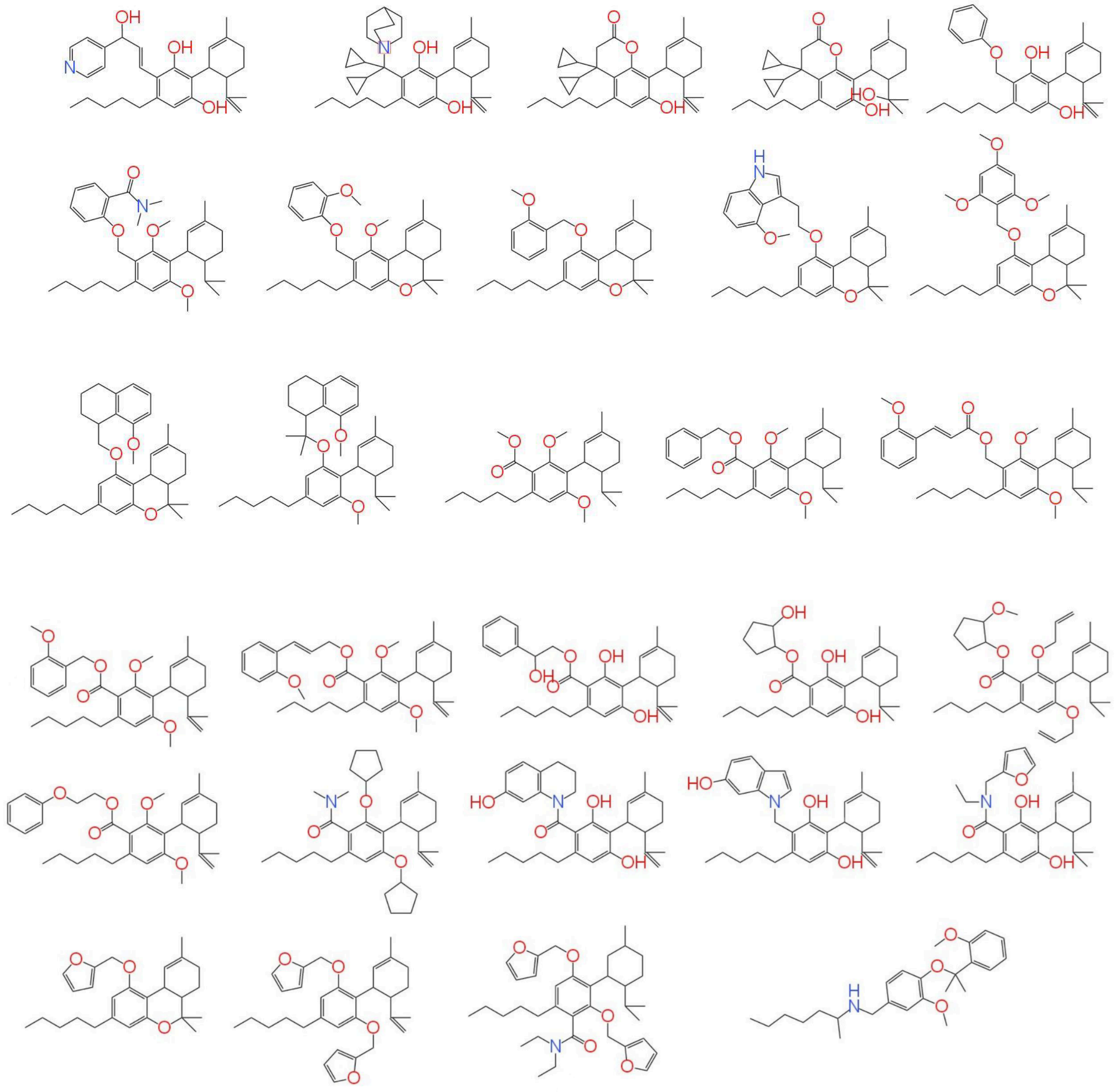
To obtain semi-synthetic derivatives of CBD, CBDA is extremely accessible and convenient, the carboxyl group of which can be used in a number of reactions and transformations to obtain highly active analogues of CBD. This is the production of amides, the conversion of carboxyl into a halogen alkyl radical with subsequent alkylation by the amino group, indole or phenolic group, this is the conversion into a keto group and subsequent condensation with aldehydes and ketones, this is esterification and reaction with magnesium organo-alkylators and much more.

To obtain highly active (dosage starting from tens of micrograms per 100 kg of live weight) derivatives of THC or CBD, it is enough to introduce minor changes to the structure, for example, to increase the tail part and add several double bonds or their pharmacological analogues to it, which is demonstrated by some existing derivatives of THC.

Since in the work we are talking about more serious changes, with the right drug design, activity and selectivity can be at the maximum level. This is not an end in itself, but it is an important step in obtaining more effective derivatives of CBD, because for a powerful anti-cancer effect, CB-2 receptors must experience a powerful, shocking and long-lasting effect.

The diagram shows some easy-to-obtain derivatives that can have high affinity and selectivity for CB-2 receptors, including THC derivatives with additional hydroxyl groups:

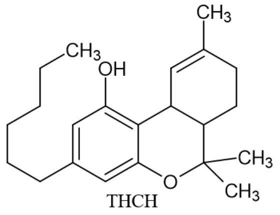




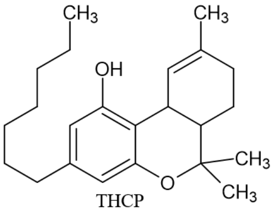
As shown in the diagram, chemical transformation of cannabinoids can be realized by simple and clean methods of pharmacological synthesis, starting from the simplest one-step amides, ending with esterification and alkylation, condensation and total synthesis of pharmacological analogs (last structure in the list).

This work demonstrates a new degree of freedom in the synthesis of highly active cannabinoids, based on rational drug design and clean methods of organic, pharmacological synthesis.

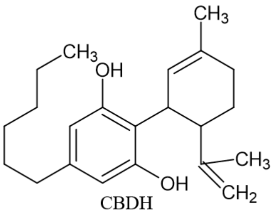
# The biosynthesis of the cannabinoids CBDH, CBDP, THCH, THCP.



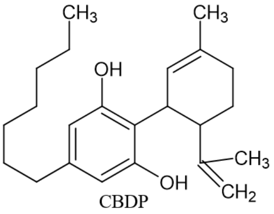
THCH



THCP



CBDH



CBDP

Selective CB-2 cannabinoid receptor agonists, such as CBD, are promising anti-cancer agents. Cannabinoids have several mechanisms of action, including promoting the activation of anti-cancer immunity, which is very promising. CBD is being extensively researched for its anticancer activity when mixed with THC and other cannabinoids, in a variety of cancers. But given that CBD is relatively difficult to synthesize, only a small number of CBD derivatives have been studied, although they have shown satisfactory activity.

It is possible to simplify the synthesis of CBD derivatives using biological methods of synthesis. In particular, possible, the simplest method is the introduction of biosynthesis precursors of CBD derivatives, as well as THC and other cannabinoids, into hemp living tissues. For example, spray flowering cannabis with heptanoic and caprylic acid to produce THC-H and THCP and their cannabidiol counterparts.

If marijuana uses acids with longer carbon chains instead of hexanoic acid, as a result, predominantly more powerful mimetics will accumulate. This is important for its anti-cancer properties, as THCP is 33 times more potent than THC, meaning that CBD, with a seven-carbon tail, could be a very potent CB-2 receptor agonist.

Given that there are already varieties of marijuana that produce exclusively CBD, the biosynthetic method for the synthesis of CBD derivatives seems to be extremely affordable, which can give a new impetus to further research and accelerate the development of highly active CBD derivatives.

Also, the biological synthesis of THC and CBD derivatives is extremely low-cost. Thus, biological synthesis wins in all possible indicators, including such indicators as impurities in the substance, because biosynthesis gives impurities from a number of cannabinoids, while chemical synthesis gives impurities depending on the chosen synthesis strategy, and thus a chemically synthesized substance can contain a large spectrum impurities, including unsafe ones.

In favor of the fact that marijuana can involve other acids in the biosynthesis of cannabinoids, the fact that THC with a tail part of the molecule equal to 4 and 2 carbon atoms was found in some Afghan and Indian strains of sativa. At the same time, the concentration of such substances fluctuated around 50% of the mass of all other cannabinoids, as well as the fact that THC-H and THCP were found in trace amounts in marijuana in some other varieties. All this suggests that marijuana is extremely promising for the production of substituted cannabinoids, including the use of spraying flowers with acids with an increased long chain, which, as you know, is extremely easy to confirm or refute.

Of course, it is worth noting that such an extremely simple, affordable and pure method of obtaining highly active cannabinoids, such as THC-H, which has a long euphoric effect, can also greatly change the recreational cannabinoid market, the cannabis market. After all, we are talking about natural cannabinoids that were found in marijuana and which are already in demand in the cannabinoid market as more recreational and euphoric.

Likely, available biosynthesis of highly active THC and CBD derivatives could significantly change the market for anti-cancer as well as recreational cannabinoids in the near future. This work can serve as a trigger for future changes, and aims to give impetus to research in the field of anti-cancer cannabinoids, increase the culture of knowledge and scientific approach to marijuana and its products.

# Glutamic acid derivatives as anticancer agents.

It is known that glutamic acid is involved in the nutrition of cancer tissue, it is also likely that glutamic acid is an important source of nutrition for cancer cells bypassing fats and sugars, which may be the reason for the low effectiveness of strict diets in oncology practice.

Glutamic acid is not essential and, theoretically, can be synthesized in the body and absorbed by cancer cells in significant quantities, being a source of energy, nitrogen and simple carbohydrates to maintain homeostasis and growth of cancer tissue during long-term strict diets.

At the same time, cancer cells are rapidly dividing and have a high energy metabolism, which makes them related to bacteria, which are often more sensitive to chemotherapeutic agents and antibiotics. The latter makes it possible to develop a design for a chemotherapeutic agent based on the structure of glutamic acid, because the cytotoxic effect of such drugs will be much more pronounced in relation to cancer cells.

Also, the design of such substances can have many levels of complexity, despite the simplicity of the glutamic acid structure.
For example, to create high selectivity, it is possible to implement structures based on quaternary ammonium salts, this will allow the drug to pass the blood-brain barrier worse, and also to linger in tissues, organs, injection sites, inhalation or external application.
It is also possible to enhance the apoptotic properties of the drug by including a fragment of essential oils in the structure, thus using the pro-glutamine core as a delivery vehicle. Such structures can be simple derivatives of glutamic acid, but they can also be deeply modified structures that are not related to amino acid derivatives, but functionally active, as well as biostable, which is very important in the development of functional substances based on rapidly catabolizing biological molecules.

The main proposed mechanisms of action of glutamic acid derivatives, accumulation at points of increased consumption and blocking of glutamic acid metabolism processes, direct chemotherapeutic and apoptotic effects, a combination of the above mechanisms.

Glutamic acid derivatives with altered molecular functionality can significantly reduce the absorption of glutamic acid by cancer cells. At the same time, quaternary ammonium salts often have sterilizing and chemotherapeutic potential due to their ability to destabilize ionic processes in cell membranes. Thus, both the transport of substances and the ability to absorb glutamic acid can be disrupted.

Pro-terpene derivatives of glutamic acid can also have high apoptotic activity. Such substances can combine the functions of blocking glutamic acid and the pro-apoptotic action of some terpenes, and some lipophilic terpenes can slow down nuclear processes in the cell, affect cell proliferation, and some others.
The overall effect of such complex drugs should be made up of the range prescribed in the structure of a specific drug. For example, structures that do not pass the blood-brain barrier may not affect the central nervous system, but substances that pass the blood-brain barrier can affect the central nervous system and possibly have a sedative or stimulating effect.

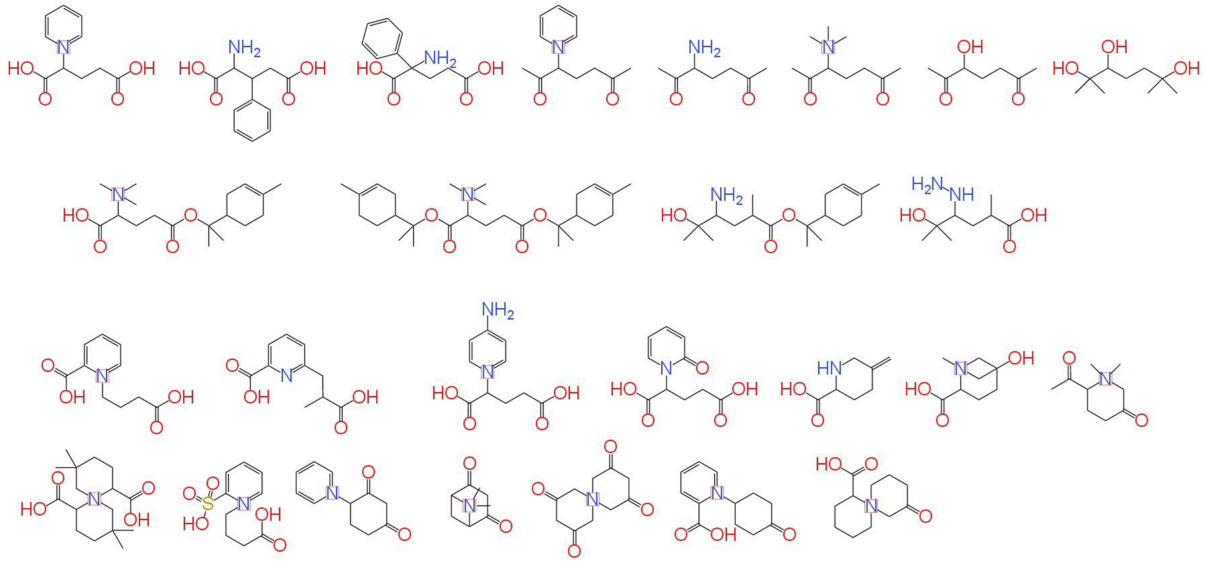
In the latter case, it is more difficult to predict the reaction of the nervous system to the drug, since such factors as affinity for glutamate receptors in the presynaptic cleft, the ability to influence MAO and reuptake, act as an agonist or antagonist in the central nervous system are added.

The reaction to the drug can be both sedative and stimulating, as well as relatively neutral.

Also, in case of high accumulation of the substance in cancer tissues, but low anti-glutamine effect, it is possible to use the pro-glutamine profile of the molecule as a delivery method. In this case, the drug delivery will be effective during a strict diet and have only pro-apoptotic potential, without affecting the metabolism of glutamic acid, which can be useful in case of brain tumors or to prevent some possible side effects.

All the above main points have been carefully drawn in the diagram. The diagram shows a list of structures from the simplest derivatives to complex and multifaceted rational design of small molecules and to a utilitarian compressed format taking into account the features of pharmacological chemical synthesis.

Examples of structures:



# Part two.

# Post-microbiological antibiotics and bioavailable complex bioactive structures.

1.Selective denaturation of the protein of the main enzymes of the pathogen as a  fundamentally new level of antibiotic development strategy. p. 35

2.Pseudo complex compounds on biopolymers. p. 37

3.Several primary strategies for obtaining new antibiotics and antiviral drugs using pseudo complex compounds on biopolymers. p. 41

# Selective denaturation of the protein of the main enzymes of the pathogen as a fundamentally new level of antibiotic development strategy.

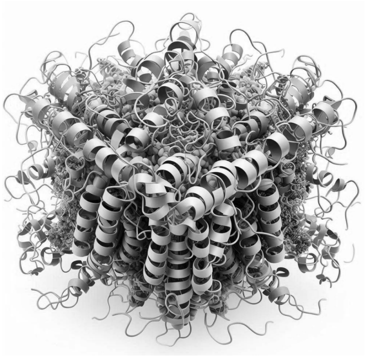


Illustration of the 3D structure of a protein as represented by a non-specialized, free AI.

Insufficient selectivity and the emergence of resistance to antibiotics is caused by their fundamental mechanism of action, borrowed from the world of micromycetes and natural antibiotic substances, which suggests the theoretical possibility of obtaining new qualities at new levels of complexity in the development of antibiotic substances.

One of these new and completely alternative principles to classical antibiotics is the forceful effect on the peripheral framework of the main enzymes of the pathogen, which can lead to irreversible denaturation of the protein structure.
As is known, denaturation of proteins and enzymes is one of the most effective methods of sterilization of microorganisms, but in known methods of application it is completely inappropriate because it is fundamentally devoid of any selectivity.
It is probably possible to correct this shortcoming by armed with advanced methods of drug design and information processing using artificial intelligence.

It is technically possible to denature an individual protein with high selectivity and efficiency, this is feasible due to the sufficient energy of van der Waltz forces that small affinity molecules of a special structure can impart to the protein molecule. Especially if these high-affinity molecules work together and hit the protein in a vulnerable spot, which is most prone to folding the entire protein structure under a targeted force.

Modern drug design methods are capable of recognizing and analyzing the required energy and point of application of pressure, creating a three-dimensional diagram and selecting selective affinity molecules for attack.

Such an antibiotic at a new level of influence does not necessarily have to consist of one active substance, to carry out such a complex operation, several or even several dozen substances may be required that will attach to the critical points of the enzyme and push it to a fatal irreversible change in configuration - in fact, to denaturation inside cells.

Similar processes occur in nature:

Prion proteins, irreversible MAO inhibitors, snake toxins, aspirin and even the first antibiotic, penicillin, are capable of irreversibly inactivating proteins. But only prion proteins are capable of changing the structure of proteins that do not have an active center, the rest are bound to the active center by a coenzyme. Prion proteins(cellular Prion Protein) tend to transition to an irreversible configuration(scrapie Prion Protein), so a certain number of prion proteins trigger a chain reaction. Although there are many examples of such reactions of a substance with a protein in nature and pharmacology, these are mainly covalent reactions with a coenzyme, in fact, this is one of the variations of antivitamins. To implement a full-fledged irreversible denaturation of selected basic proteins of a pathogen, more precise and verified, complex and subtle energies are needed, the energies of Van der Waals forces, a complex rational and machine drug design and a lot of time and effort.

Thus, a fundamentally new level of antibiotics can be formulated and tested on the existing material base and mathematical models, it is also possible that the first steps in this direction will not require unnecessary costs and effort, for example, if this principle is emulated, having received confirmation of the prospects of such a path.

Possible prospects for such antibiotics:

Since the active substances have affinity for the peripheral framework of the enzyme, this means that their affinity extends exclusively to selected amino acid sequences at certain distances between each other, this is always a unique code of radicals, which guarantees an unprecedented, maximum theoretically possible selectivity of action.

Lack of tolerance and resistance, since the main enzyme is not partially blocked, but is irreversibly disabled, completely new qualities regarding the adaptation of the pathogen are possible, and it is even possible to overcome the point after which tolerance and resistance become impossible.

Antibiotics at a completely new level of functioning are likely capable of demonstrating completely new levels of safety and effectiveness. Fundamentally important parameters are extremely high selectivity and extremely low potential for the emergence of resistance. Both the first and second are acceptable in theory, it remains to move on to practice.

# Pseudo complex compounds on biopolymers.

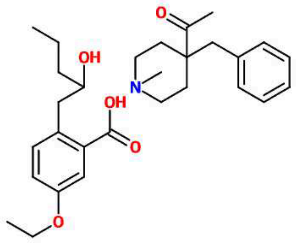
Biological polymers do not always have a repetitive structure, they are often complex and individual patterns of bonds and radicals. A good example of such biological polymer surfaces is the receptors of neurotransmitters, hormones, and the surface of enzymes.

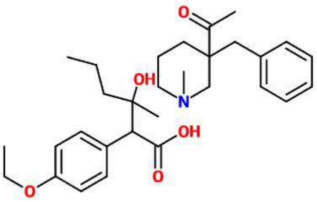
Such complex and non-repeating sequences of radicals contribute to the sorption of complementary substances on their surface, in their specific area.

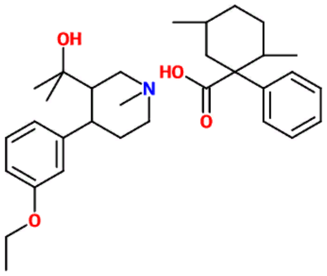
Thus, the physicochemical feature of the surface determined its role in nature and gave us the opportunity for a complex drug-design associated with hormones, neurotransmitters ..

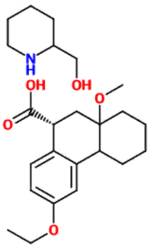
Could the special delicate complementary bonds between the target and the substance give birth to a special kind of compounds, even more outlandish bonds than the complementary bond?

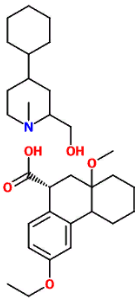
This question will probably be answered if we measure the opioid activity of the organic salts presented below:

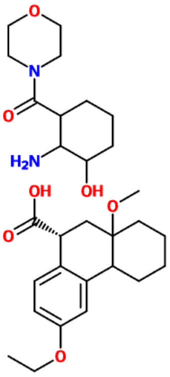


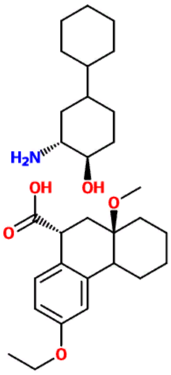


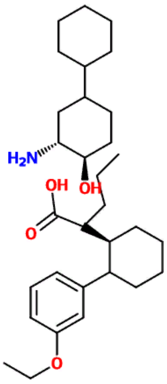




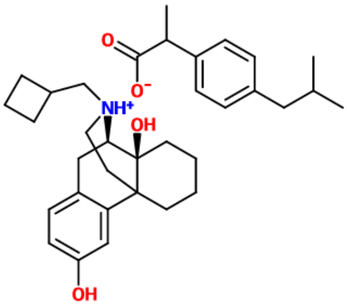






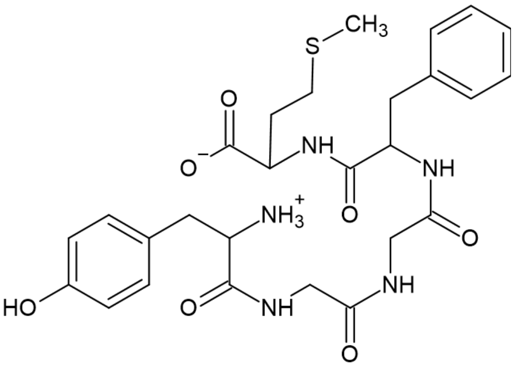


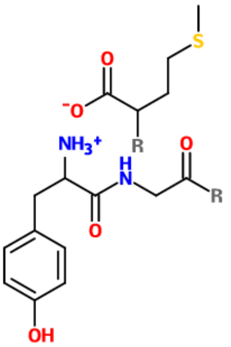
As you can see, each presented organic salt is connected mainly by only one ionic bond, and having penetrated into the enkephalins receptor zone, it will be separated by the repulsive forces of the complementary radicals of the receptor. But this will not happen instantly, this is indicated by the higher narcotic activity of butorphanol used together with ibuprofen:



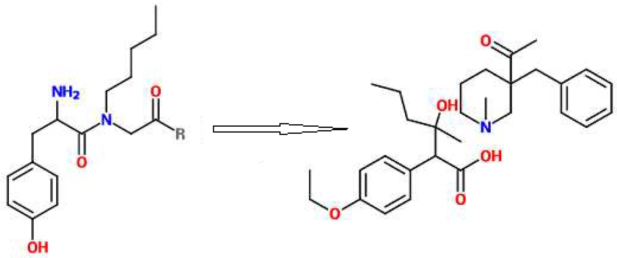
Also on the presented chemical structures you can observe the propyl radical, which is a radical complementary to that part of the target that binds the tail of leucine or methionine.

Considering the fact that leucine or methionine in the structure of enkephalins(incorrect volumetric structure, hydrogen bonds are not taken into account) is the final amino acid that comes in three-dimensional space from the side of phenylalanine and closes the chain with an inner salt with an amino group of tyrosine:





We can conclude that in the case of placing a pro-leucine or pro-methionine radical in that part of the salt that corresponds to the tyrosine part of enkephalin, we can weaken the separating forces on the surface of the receptor:



Considering also that cyclohexane in this case plays the role of a cyclic hydrogen bond mimetic in the structure of enkephalins, and this also contributes to the compression of the receptor surface, we will probably be able to significantly reduce the tensile forces of radicals on the receptor surface.

As a result, the organic salt will be held on the receptor surface by additional forces, and the sum of all the forces involved in holding the molecules together may exceed the separating forces for some time.

Thus, with the right thing drug design, we can get substances that, being on biological polymers, will behave like complex compounds. The absence of a direct chemical bond does not negate the practical prospects of these pseudo-complex compounds. Moreover, such substances can have great advantages:

Since we are talking about self-assembling structures, which can consist of many substances, and in contact with the target, assemble into a puzzle of a given structure, and at the same time demonstrate increased strength and stability, high sorption capacity. Such pseudo-complex substances can be used as mimetics of complex protein transmitters and hormones, penetrate deep into tissues, and perform a complex mimetic function.

These can be drugs that trigger complex processes in cells and the body, the regulation of metabolism and growth, it can be neuronal growth factors, as well as apoptosis provoking complex mimetics.

This work is a preparation for the first step towards the development of drugs based on pseudo complex compounds on biological surfaces. The above examples of salts have a relatively simple structure for carrying out chemical synthesis, the activity of this group of substances is easy to measure, and thus the effectiveness of the pseudo complex bond can be estimated.

The ionic bond in such complexes is not necessary, but in this case the enkephalins are too small in structure and do not give much room for the variety of radicals used.

Despite the subtlety of such a design and doubts about the possible effectiveness, there are examples testifying to a hypothetically huge potential:

Such examples would be the excellent mimetic properties of some simple terpenes of plant essential oils. For example terpineol or menthol, these are small substances, but they are weak mimetics of enkephalins. Also many immunomodulatory terpenes, which are in fact tiny substances, but they are probably very effective at performing mimetic pro-protein functions, and thus activate immunity. Terpenes in this case are not pseudo complex substances. They only have a pro-peptide weak mimetic nature, but at the same time they are poorly soluble in water. Water pushes these molecules out, and they are more readily absorbed on a suitable target. After all, one drop of essential oil can transform the human body into a saturated “solution of essential oil”.

Accordingly, with successful work, it is possible to obtain a capsule of several or ten substances, and this amount of substances may well be enough to saturate the human body and carry out the necessary work at any point in the body.

Separately, mention should be made of going beyond the biological capabilities of pathogens in the development of antibiotics based on such pseudo complex substances:

In the above mentioned work, possible directions in the development of antibiotics based on similar substances were indicated. And this can be extremely important, with some complex approaches, in order to develop resistance to an antibiotic, the pathogen would have to carry out probably an unrealistically large number of mutations.

That is, perhaps pseudo-complex compounds are capable of setting such a high bar in the design of antibiotics of the future that the pathogen will biologically not be able to carry out the chain of necessary mutations to develop resistance. There are no such antibiotics in nature, since biological methods of construction are insufficient for their construction, there are not enough mutations in the mechanism of antibiotic synthesis...

And so, the increased activity of the above examples of organic salts can open the way to high bioavailability of complex molecules and opening super antibiotics.

# Several primary strategies for obtaining new antibiotics and antiviral drugs using pseudo complex compounds on biopolymers.

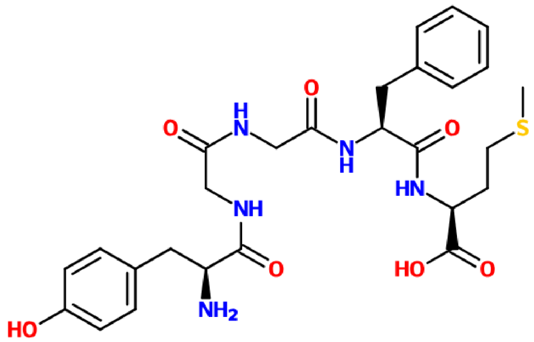
Modern antibiotics have evolved from microbial and have a number of inherited deficiencies. This is the impact on the active center of the target (one of the main enzymes of the pathogen), as a pseudo-brick, pseudo RNA segment, DNA, amino acids ... This has a point impact on the function of the enzyme. And also modern antibiotics, like micromycetes, imply the action of a single substance or several substances, but without complex pharmacological strategies. This also narrows the already indicated action.

This principle works well in relatively simple microbial battles, in the natural habitat of micromycetes, but in more complex conditions, there are multiple disadvantages of micromycetes antibiotics.

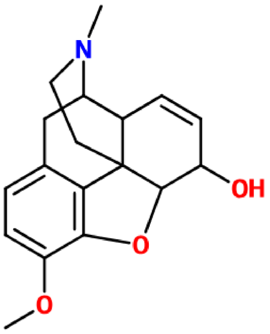
Calculated by nature as a tactical weapon in the war for the territory of micromycetes, the microbial antibiotic (and a synthetic antibiotic in the spirit of the pharmacology of micromycetes) is not capable of a long-lasting and lasting effect. It has a slight selectivity, because its structure mimics substances that take a large part in the living tissues of any organism - DNA, RNA, Amino Acids, Cell wall fragments ... This approach is better implemented for primitive biological objects that do not have many physical goals and therefore, there is less chance of side effects. This approach is also suitable as a tactical method, the drug which will be replaced by a new one.

In addition to micromycetes, there are still some natural sources of antibiotic substances, these are plants, their essential oils, terpenes and terpenoids. Essential oils of plants often have a bactericidal potential, also have an mobilizing immunity nature or allergic nature of the action. This is easily explained by the fact that the terpenes have a pro-peptide structure .., and despite their low molecular weight, they act as a signal close to the pathogen protein, allergen, part of the membrane of the microorganism ... The structure of essential oils is faceless, there are no specific references to that or another type or type of substances, but there is a slight and non-selective effect of them. For example, menthol, it is a light central anesthetic that acts on K-opioid receptors, like Salvinorin. Terpineol and similar terpenes have little effect on the M-opioid receptor, and block the center of cough, have a mild effect, increase endorphin innervation, removing stress triggers, and as a result, increase immunity. Terpineol is much weaker than the benzoic analogue of salvinorin(herkinorin). These substances have a low molecular weight, but act as mimetics of short peptides - enkephalins. Some of them were used in pharmacology as an antitussive, as a replacement for codeine. Codeine is much more massive than terpineol and carries much more structural information.

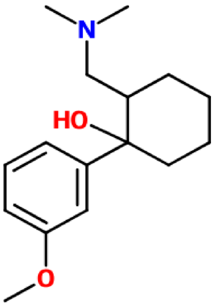
Examples of similarity of substances complementary to the surface of the receptor recognizing enkephalins:


O
H
N
O
N
H
O
S
NH
HN
O
HO
O
HO
NH2

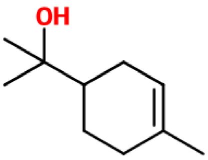
Met-enkephalin



Codeine

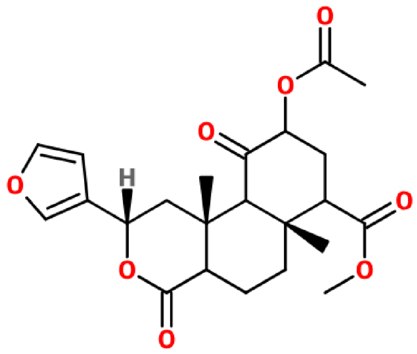


Tramadol

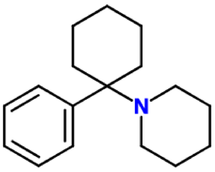


α-Terpineol

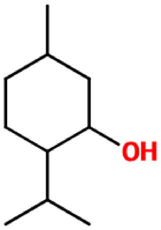
(-OH group in the case of enkephalin mimetics, plays the role of an amino group)



Salvinorin A



Phencyclidine



Menthol

Met-Enkephalin and Terpineol clearly demonstrate how simple essential oils, terpenes, and heavier molecules, terpenoids, manifest themselves as small peptides. The receptor perceives a small terpineol as enkephalin, which means that a weak complementary bond arises between the receptor and terpineol.

In the context of this work, a weak complementary connection is a key factor - this is the power that we can apply to any target, hormone receptors, immunity receptors, receptors on the surface of viruses, even selectively a separate protein or enzyme, its specific part, or surface an organelle.

The fact that enkephalin mimetics have a psychoactive effect greatly simplifies possible research: if it is necessary to compare the strength of the antinociceptive effect, a simple test to overcome the pain threshold in a vivarium is sufficient.

The power of complementary interactions can be applied to any target, as the immune cell does - it attracts a selected fragment of the target using a complementary set of radicals, which ultimately tend to stick together.

The strength of weak complementary interactions (interactions without stable chemical bonds) may be enhanced. This is possible by increasing the amount of structural information, or using a very complementary radical. An example of such a radical is methyl-fentanyl, carfentanil, etorphine. Etorphine has a radical simulating methionine in the state of a closed inner salt of enkephalin, as well as the -OH group which plays the role of an additional variant of reading etorphine sorbed on the receptor. Examples with enkephalins are illustrative, and since the analgesics and antitussive drugs are numerous and their structures are visual derivatives of endorphins, this makes analgesics a good tool for demonstrating the complementary linkages of short peptides.

It is also possible to absorb areas of the main enzymes of pathogens. Small sections, chains of sections, separate sections, glue pieces spirals, insert a wedge, insert a sticky wedge.

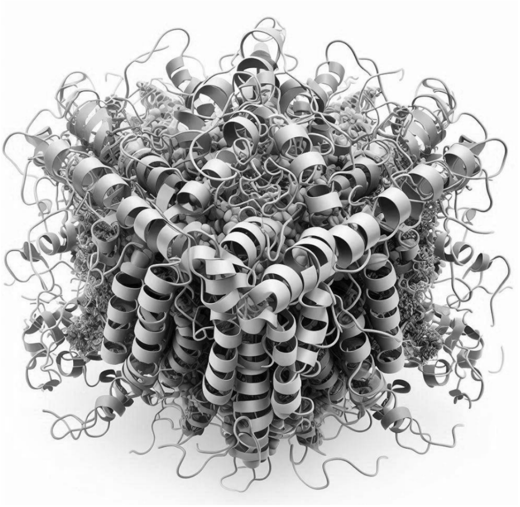


Illustration of the 3D structure of a protein as represented by a non-specialized, free AI.

In order to get substans selective for the target, but inert to the human body substances, we need to use nuclei of a different nature than DNA, RNA, Amino Acids, Vitamins, Carotenoids and Fragments of the membranes of organelles.

The fixation of the enzyme means that it cannot change the conformation, that it is incapacitated, since for each operation of the enzyme there is a corresponding geometric configuration of the protein. This is the part of the working action of the enzyme for which the protein is responsible, it changes the configuration for the sorption of various elements in the active zone, as well as for combining the reactants, to transfer momentum to them. This is an energy balancing with a variety of form and energy configurations provided, the part that remains behind the scenes of pharmacology.

All configurations have energy pits and elevations, as well as positions between them. Our goal is to choose the most energetically and structurally advantageous option in order to stitch it at the optimum points of contact. This method involves a huge area of complementary interaction, at the most energy-friendly points, multiple, from several substances to several dozen, tremendous synergy, and selectivity over many parameters. It's just like instead of spoiling one brick of LEGO, you tie a child with a rope. He can only hold two bricks in his hands, but he cannot build anything from them. A standard antibiotic is similar to only one broken brick, which makes it difficult to build a structure, but sooner or later the hand takes the right brick instead. In our case, there is a possibility of a complete stop of the main processes of the pathogen.

Because each protein in nature is individual, each section corresponds to an individual set of complementary substituents, the substances selectivity can increase to the maximum. It can be different nuclei, hetero-chemical, like alkaloids, essential oils, terpenoids .. Each option has advantages - hetero chemical substances easily modify with radicals. Hydrophilic substances are convenient for injections. Lipophilic substances can be very sticky because they are poorly soluble in the medium and a small amount of essential oil can turn the blood into a saturated solution of terpenes.

Just as we have moved away from "microbial thinking," it is necessary to avoid chemical thinking in this area. Since hetero chemical structures are not like proteins or fats, it is often difficult to use them in the development of peptide mimetics or fat derivatives. An example would be analgesics and synthetic cannabinoids, not all heterocyclic cannabinoids show good results, both when evaluating the analgesic action and when evaluating anticancer activity. The same is true of central analgesics. Hetero Chemical compounds among analgesics are very few, because a small error in the drug design can lead to the suppression of the respiratory center.

Because large molecules are difficult to dissolve and poorly penetrate biological barriers, substances should have a small molecular weight. This is easy to implement, even if the area attack is large, using several substances that are closely interlocked in both the target and among themselves. Thus, it is possible to achieve the similarity of polymer self-assembly on the target surface.

A similar simulation of self-assembly can be used in immunological preparations. For example, in the development of anti-HIV immunoactive substances. This can be realized as a substance that fits tightly on the cap of the HIV fungus (the complementary part of the molecule), and the other part of the molecule can have a radical in the form of a small portion of pyrogenic polymer. Since there are a lot of caps on the surface of HIV, and all of them have a stable and specific structure.

A whole forest of monomeric particles on the surface of HIV can make such a move. One fragment of the pyrogenic polymer alone does not provoke an immune reaction, but the forest of monomeric fragments accumulated on the surface HIV will essentially represent pyrogen and the reaction should follow.

It is also possible with the help of such techniques to influence specific cancer tissues. It is also probably possible to mimic the effects of complex hormones, a large mass of which cannot allow the use of one active substance. Run apoptosis of cells, pathogens..

The method of complementary impact is an endless list of manipulations that can be carried out based on the calculations,only a part of which was described in the works above. The theory and technique of such calculations is the pinnacle of modern knowledge in the field of drug design.

Deep work on subtle connections, in the long term, is a molecular manipulator that performs an almost unlimited number of jobs, of any complexity, with unprecedented precision.

# Part three.

Pharmacology and drug design, new structures, pharmacological schemes of substances, drug projects, as well as inclusion of such topics as microbiology, genetics, light industry..("Total Drug Design")

1. Alpha-terpineol, butanol and isoamyl alcohol as pro-opioid agents in whiskey and gin. p. 48

2.Cannabis as a convenient agent for the production of new pharmacopoeial cannabinoids. p. 51

3.The pharmacology of Cardamom (α-terpineol) as an ultralight opiate. p. 53

4.Complementary to enkephalin receptors. Search for alternatives to fentanyls. p. 55

5.Condensed structures like hypericin (Hypericum perforatum), but pro-serotonin in nature. Potentially as antidepressants. p. 60

6. Dopaminergic and ultra-light cannabinoid terpenes. p. 62

7. Examples of drug-design, pharmacological analogs Salvinorin A. p. 64

8. GABA active synthetic terpenes. p. 65

9. Hypothetical scheme of the pharmacology of Picrocrocin (Saffron. Crocus Sativus) and structures similar to picrocrocin. p. 67

10. Nicotine as dopaminergic. Examples are derivatives of nicotine, search structures with low toxicity and carcinogenicity. p. 69

11. Peripheral opioids and cannabinoids, local analgesics. p. 73

12. Opioid radicals in the structure of antipsychotics, anxiolytics, anticonvulsants and some others. What big pharma is hiding. p. 74

13. Physics lesson for a teacher of physics, history and anthropology. p. 78

14. Physiologically active alcohols, analgesics and dopaminergics. p. 79

15. Possible atypical kappa opioid, agonists of NMDA receptors. p. 84

16. Powdered tea from Hypéricum perforátum(St. John's) wort as a remedy for depression.
p. 86

17. Prospects for saffron as a means of increasing dopamine in marijuana users.
p. 88

18. Rational drug design on the example of light cannabinoids. p. 89

19. Simulating effects of alcohol, using μ and κ opioid active alcohols. p. 93

20. Structurally similar to stimulants and antidepressants, alcohols as substances with possible anti ADHD potential. p. 95

21. Structures close to reuptake inhibitors neurotransmitters and serotonin. p. 97

22. Substances structurally similar to LSD, tryptamines and phenethylamines.
p. 100

Substituted 1,3-dioxolanes, structures close to analgesics, anesthetics and dopaminergics.

p. 106

23. Substituted structures tryptophol, phenylethanol, 1.3 dioxolane and other neutral compounds as structures that are close to nature of psychedelics. p. 107

24. Super light NMDA receptor antagonists as promising substitutes for Ketamine and Amantadine. p. 110

25. Superlight synthetic cannabinoids. p. 111

26. Synthetic terpenes as a universal GABAergic, dopaminergic and light cannabinoids.

p. 113

27. The putative pharmacology of functional adamantane derivatives. p. 114

28. Using water-based ultrasonic electronic cigarettes. p. 115

# Alpha-terpineol, butanol and isoamyl alcohol as pro-opioid agents in whiskey and gin.

The effects of ethanol are multifaceted, since ethanol affects the membranes of nerve endings, it changes the susceptibility of receptors, promotes the release of neurotransmitters, without not-selectively affecting many neurotransmitters.

Among the dominant effects of alcohol, one can single out opioid effects, dissociative, GABA and glutamate effects, as well as dopaminergic effects.

A small dose of alcohol affects dopaminergic receptors, opioid, dissociation, excitation of glutamate receptors. A large dose enhances the opioid component, GABA and dissociative anesthesia.

The use of alcohol as a recreational drug requires the most pronounced recreational properties from the alcoholic beverage, in the context of the pharmacology of ethanol, the most pronounced opioid and dopaminergic effects.

Certain recipes, methods and excipients are widely used to correct the taste, toxic, and pharmacological qualities of alcohol.

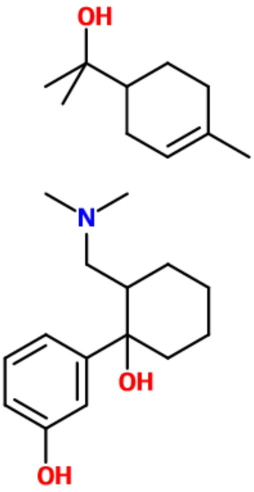
Consider those substances that are likely to enhance the basic recreational qualities of alcoholic beverages, and also have traditions of use:

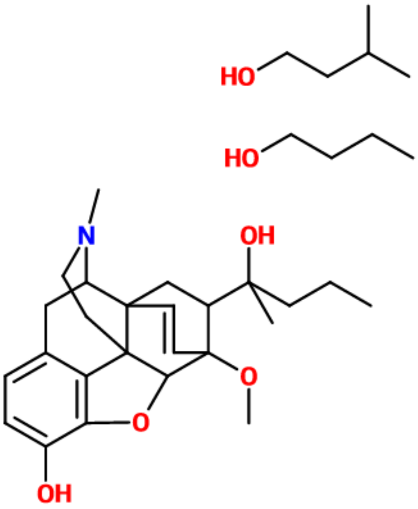
Spices Saffron, Cardamom and fermentation products such as butanol, isoamyl alcohol and their esters.

Since ancient times, saffron has been used as one of the best spices to improve the quality of wine, saffron is a dopaminergic and is definitely able to enhance the pro-dopamine effects of alcohol. Alpha-terpineol, which has a pro-opioid structure, is used to improve the properties of gin, probably as a compensation for the lower concentration of butanol and isoamyl alcohols compared to whiskey.

Butanol, low-toxic and narcotic alcohol, as well as isoamyl alcohol, is part of whiskey, in huge permissible concentrations. Isoamyl alcohol also has narcotic effects, but is much more toxic than butanol. Butanol was used in medical practice as an anesthetic.

Butanol, isoamyl alcohol and alpha terpineol are alcohols, but with a more complex structure than ethanol, this suggests that in addition to their non-selective effect on biomembranes, mimetic properties may also appear, as in complex alcohols such as lactucin, lactucopicrin, salvinorin and some others:

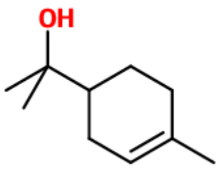


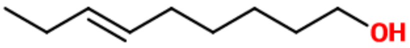


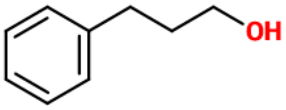
Alpha terpineol has a distant structural similarity to, for example, desmethyl tramadol.

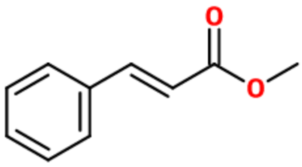
Ethyl and isoamyl alcohols have a similar structure with an important etorphine radical.
This radical mimics the enkephalin fragment in the region of the amino group, while enkephalin is in the internal salt state and the terminal amino acid is located next to the amino group of tyrosine.

So, the illustration clearly demonstrates the possible pro-opioid activity of alpha-terpineol and some components of fusel oils. This could be a turning point in understanding the recreational pharmacology of spirits, and could also hold the long term for phasing out toxic impurities and use other less toxic natural alcohols:

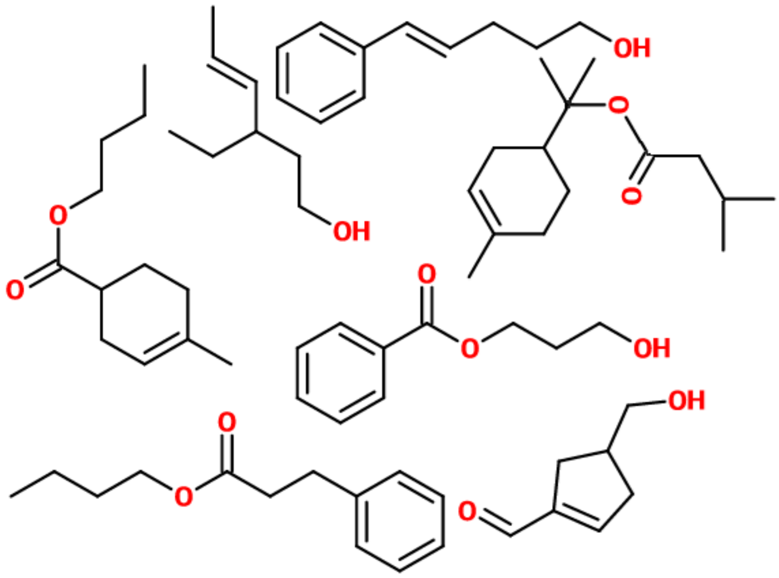








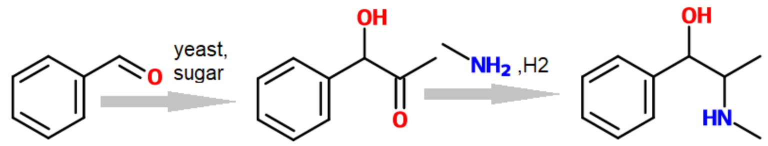
It is also possible to use semi-synthetic variations of selected natural terpenes:

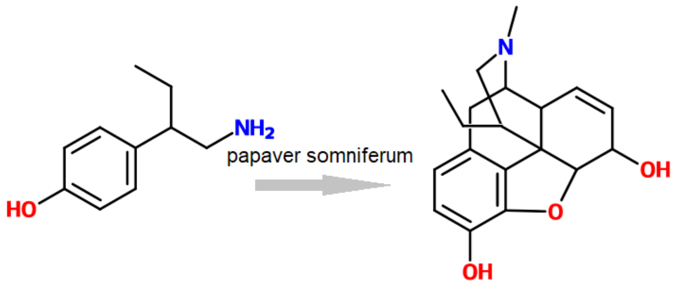

OH
OH
O
O
O
O
O
O
OH
O
O
OH
O

As well as more complex and diverse synthetic terpenes, alcohols, esthers, ethers, lactones, dioxanes and dioxolanes, which were published earlier in the author's works.

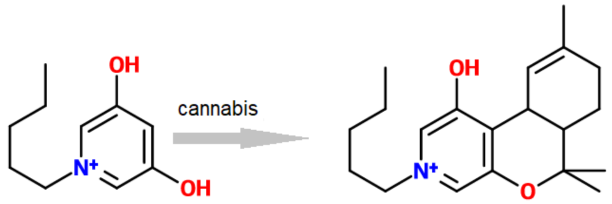
# Cannabis as a convenient agent for the production of new pharmacopoeial cannabinoids.

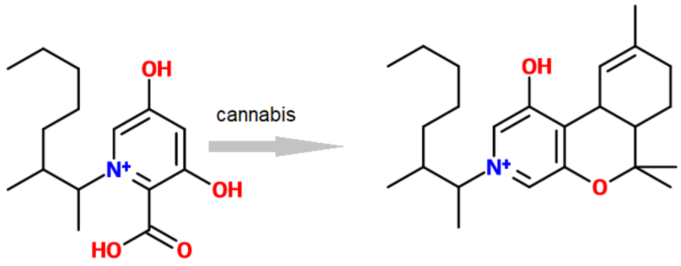
Yeast, bacteria and plants can be used to obtain pharmacopoeial preparations not characteristic of the above producers, provided that the necessary synthetic derivative is added to the substrate. This is how some drugs and substances were produced, such as ephedrine, tyrosol, high affinity derivatives of morphine, and some others. In the case of highly active end products of biosynthesis, this method can be very promising at the present time. After all, this method does not require expensive genetic changes in organisms, and is reduced to adding a reagent to the nutrient medium, or spraying the plants with a reagent:

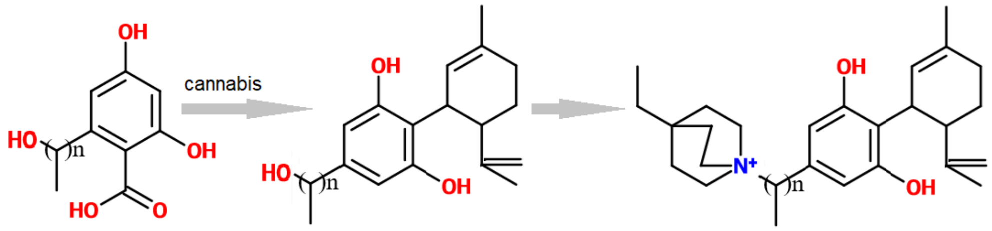




This method of obtaining drugs has a number of limitations, such as the complexity of obtaining arbitrary substances. The substance must be strictly coordinated with the biosynthesis scheme, which limits the freedom of using the method. But a number of restrictions can still be removed using a high-quality rational drug-design when developing new drugs:







THC \ CBD derivatives that do not cross the encephalic barrier.

Some non-strict compliance with respect to the initial structure can affect the rate of biochemical reactions and even block biosynthesis. But if the introduced radicals do not create spatial hindrances, do not critically affect the distribution of electrons in the molecule and the reactivity of key atoms, biosynthesis can proceed at a normal rate, and in some cases even more active than with the native predecessor.

Since plants accumulate physiologically active substances and do not have powerful mechanisms for identifying foreign substances and enzymatic systems for deactivating foreign substances, new derivatives must accumulate like native substances.

This method requires more rational effort, a more comprehensive approach, and will probably gain its relevance with the further development of pharmacology.

Inference:

Thus, innovative approaches to drug design and synthesis of substances can give very high results if implemented in a complex manner. The method of biosynthesis of modified physiologically active substances can be applied in the future with new strength and degree of complexity dictated by new challenges and trends.

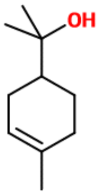
# The pharmacology of Cardamom (α-terpineol) as an ultralight opiate.

Cardamom is the second most valuable spice in the world after saffron. Cardamom strengthens the nervous system, reduces depression, relaxes and improves the quality of life. The main active ingredient of cardamom and the main component of essential oil from green cardamom is α-terpineol, up to 45%, and α-terpinyl acetate are contained. Black cardamom fruit contains predominantly eucalyptol, which probably reduces the quality of the product, eucalyptol is relatively toxic and has a completely different pharmacological profile.

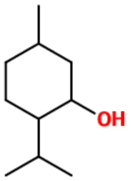
Terpineol is probably an ultralight opiate, just like menthol(ultralight k-opioid). Saffron (the active ingredient picrocrocin), in turn, is a dose-dependent dopaminergic, an effective inhibitor of dopamine reuptake.

The molecules of the listed terpenes have a very simple structure, and in the case of menthol and terpineol, they have a very weak mimetic ability due to the small amount of structural information in these molecules. Such structures have low affinity and a low ceiling of maximum activity. The former is the reason for the absence of withdrawal syndrome, the latter contributes to greater safety and the absence of acute symptoms of overdose.

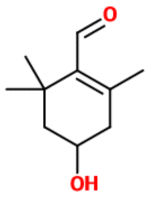
Ultralight agonists and light reuptake inhibitors share similarities with more potent substances in their category, as clearly demonstrated by the comparison diagram:



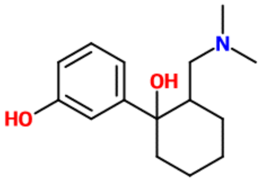
α-terpineol
super light μ-opiate



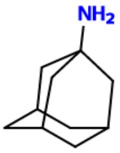
Menthol
super light κ-opiate
(NMDA receptor antagonist)



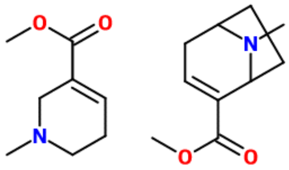
Picrocrocin aglycone
dose-dependent dopamine
reuptake inhibitor



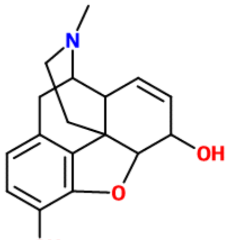
Desmethyl tramadol
opiate



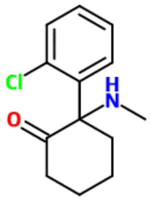
Amantadine
NMDA receptor antagonist



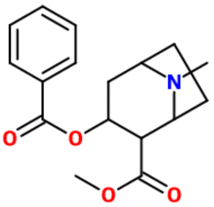
Arecoline, dehydro-ecgonine
probably partially dopamine reuptake
inhibitors



Morphine
opiate



Ketamine
NMDA receptor antagonist



Cocaine
dopamine reuptake inhibitor

Millennial use of ultralight opiates and dopaminergics does not have the many reported deaths, acute poisoning, or severe side effects that are the case with hard drugs. Such spices and preparations based on them do not require special precautions and are not dangerous for street trade. Such substances do not have a negative effect on the individual and society, do not contribute to the spread of HIV and hepatitis, are legal all over the world and are practically harmless in comparison with hard drugs.

The use of super-light, both natural and synthetic drugs for recreational purposes is a promising direction in relation to the fight against hard drugs, gangsterism reduction, the spread of HIV, and the black market.

It is also especially worth noting the fact that such terpenes are lipophilic, which makes them active in relatively small doses, and this in turn reduces the risk of side effects. A weak analgesic or antitussive drug created on the basis of amines and hetero chemical substances is often prescribed from tens to hundreds of milligrams, while terpenes are able to act starting from several milligrams. The positive aspects do not end there, often weak mimetics have a very low activity ceiling, this is the key to the absence of lethality of drugs, but such drugs are also characterized by the fact that they act from the most insignificant doses, while powerful analgesics have a noticeable effect in relatively large doses, super light terpenes begin to act from an extremely low start, being a unique tool for achieving subtle and virtually harmless effects.

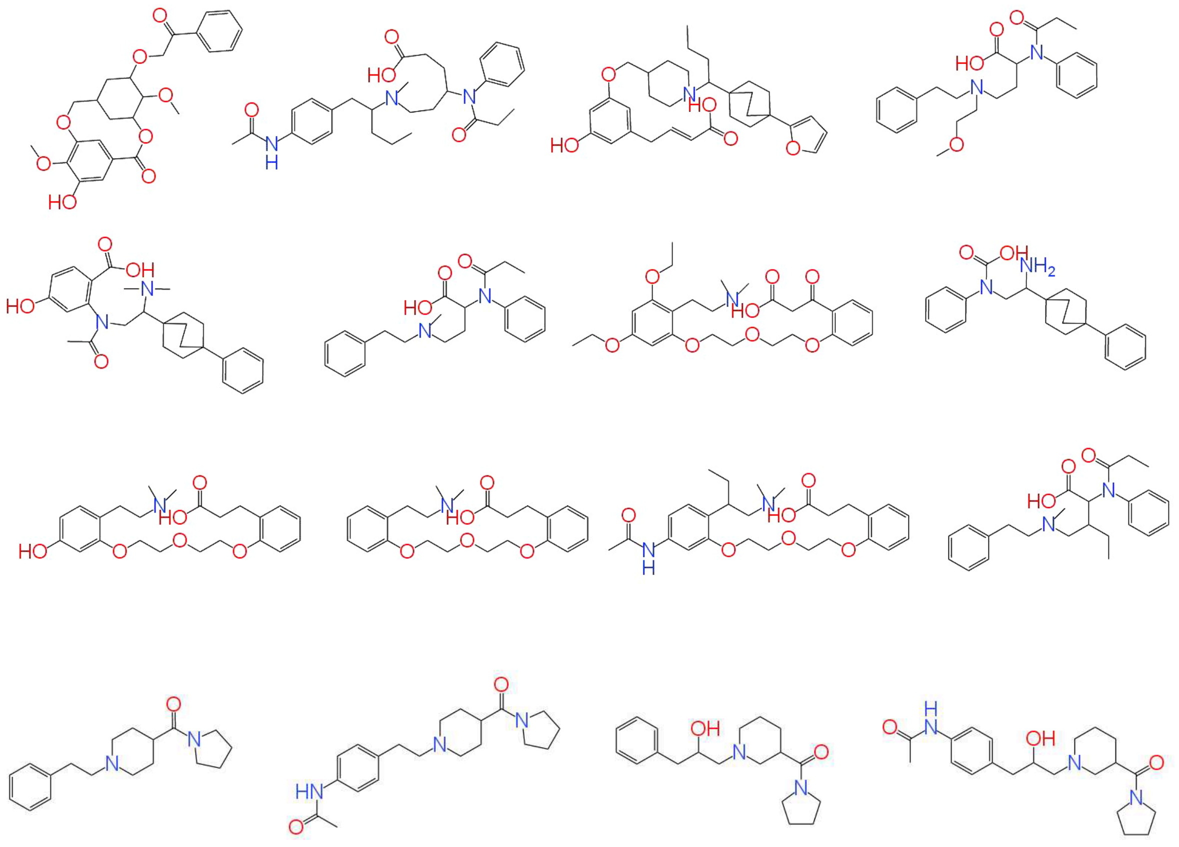
# Complementary to enkephalin receptors.

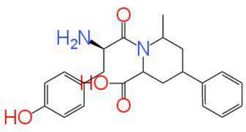
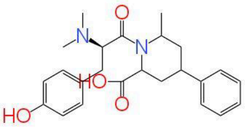
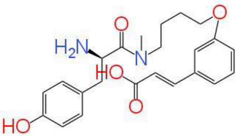
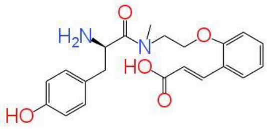
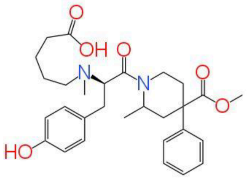
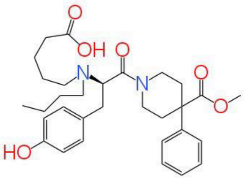
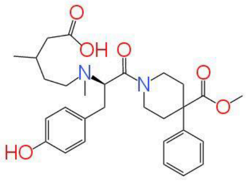
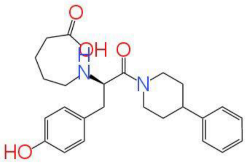
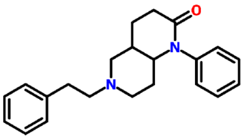
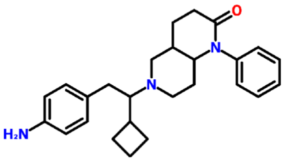
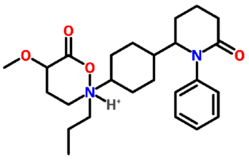
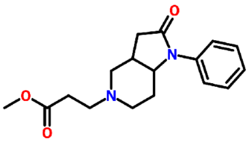
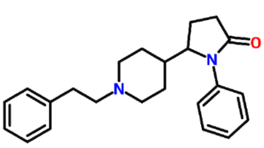
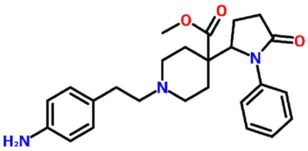
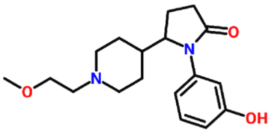
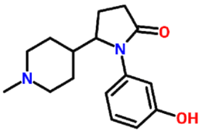
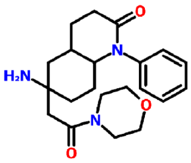
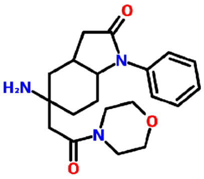
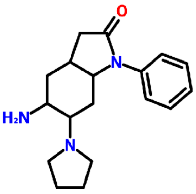
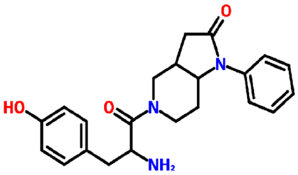
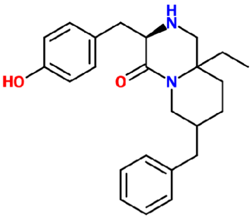
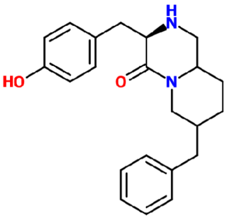
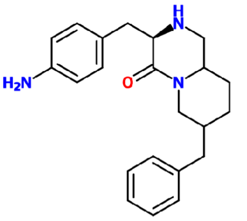
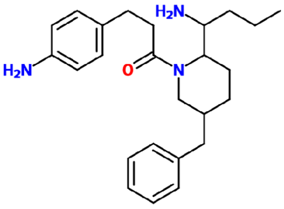
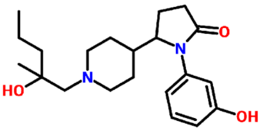
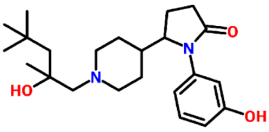
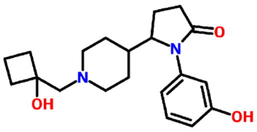
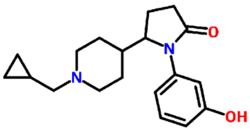
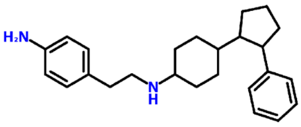
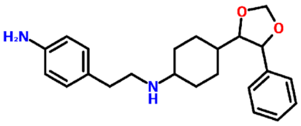
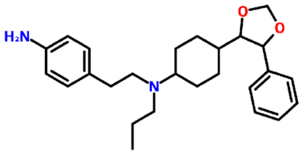
# Search for alternatives to fentanyls.

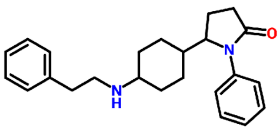
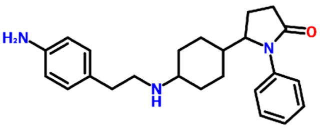
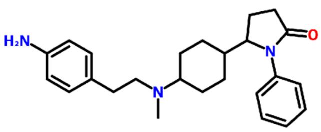
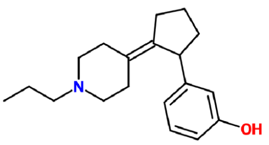
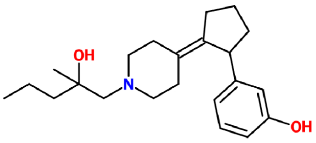
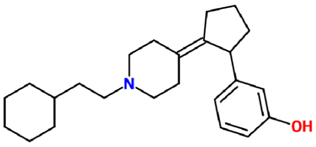
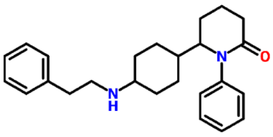
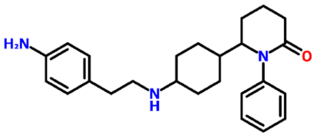
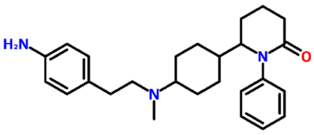
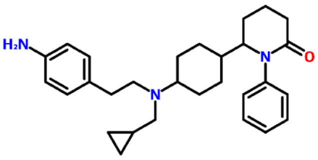
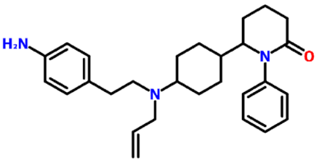
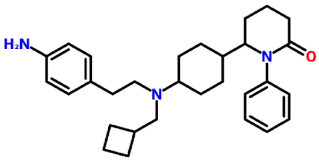
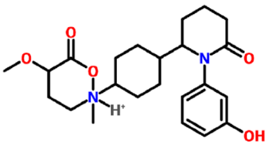
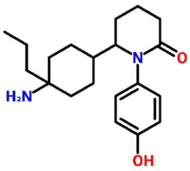
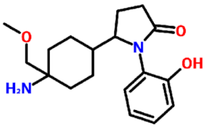
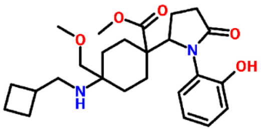
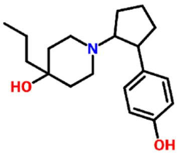
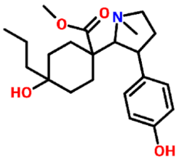
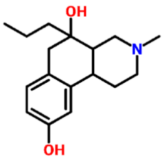
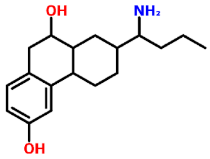
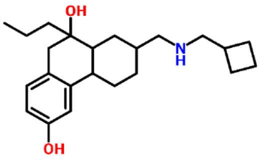
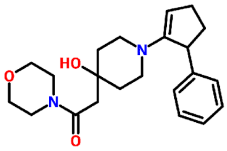
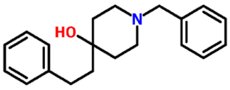
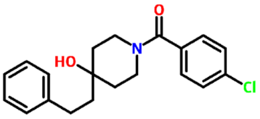
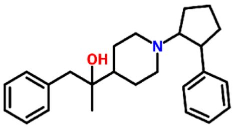
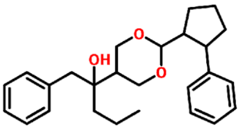
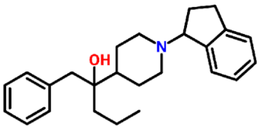
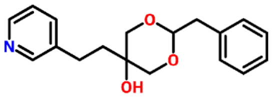
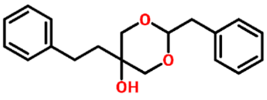
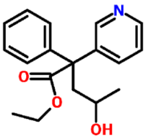
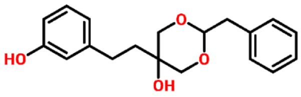
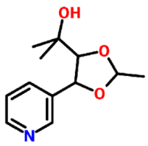
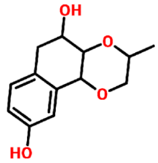
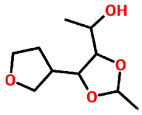
Enkephalin in aqueous solution exists in several configurations. Probably, this is connected with the form in which they bind to the receptor. Based on the configuration of enkephalin, which is close to fentanyl and pharmacological drugs developed by rational drug design. It is possible to propose an alternative chemical structure to the available fentanyl derivatives.

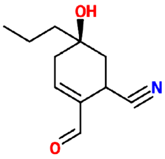
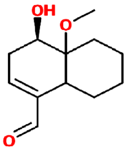
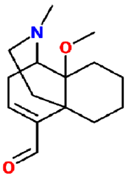
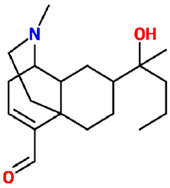
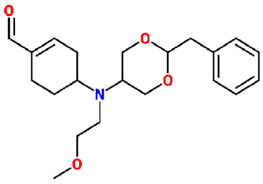
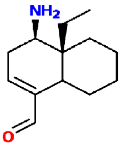
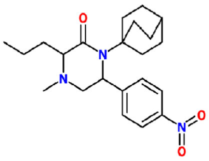
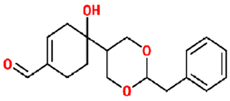
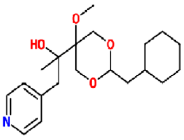
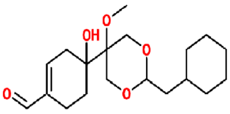
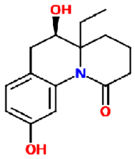
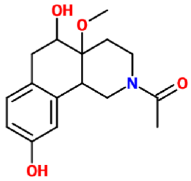
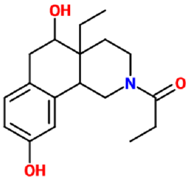
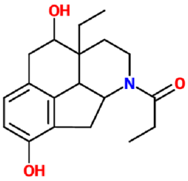
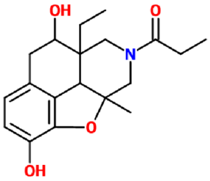
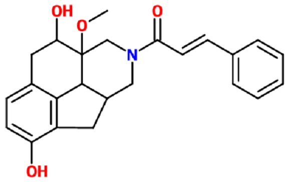
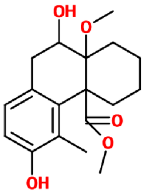
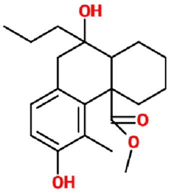
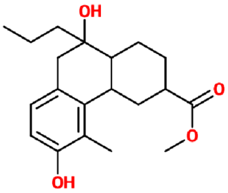
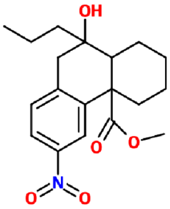
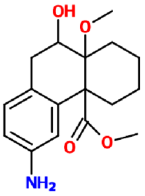
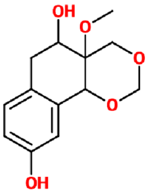
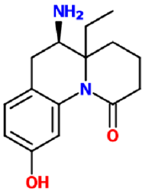
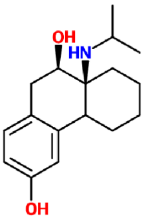
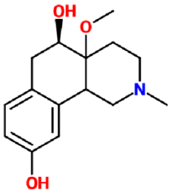
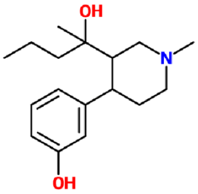
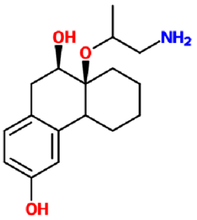
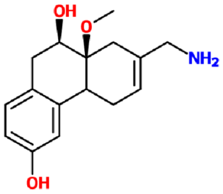
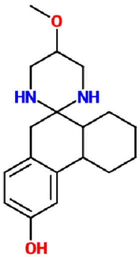
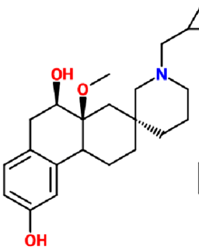
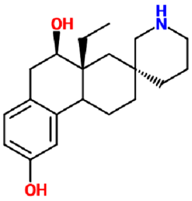
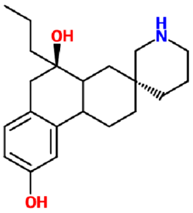
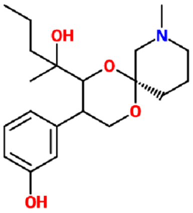
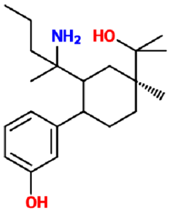
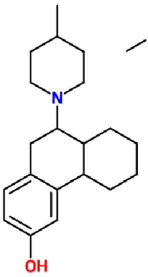
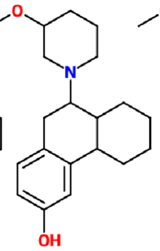
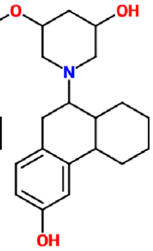
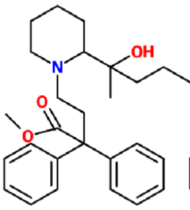
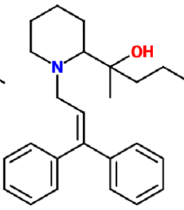
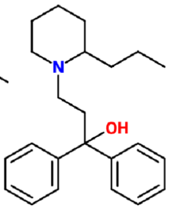
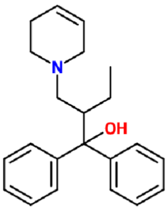
The alternative is important as a possible way to reduce lethality, extrapyramidal side effects and narcotic central effects. An important direction is the modeling of the primary amino group, because such derivatives have the potential to reduce narcotic effects, correction of the arrangement of aromatic nuclei and hydrocarbon cycles. Increase in the quantity of cycles can reduce extrapyramidal effects, also such derivatives will be significantly less accessible for illegal synthesis.

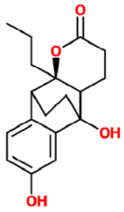
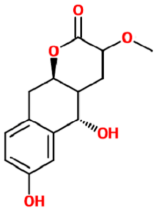
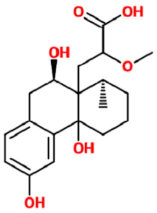
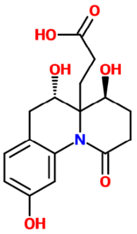
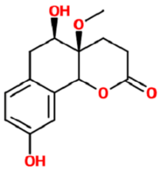
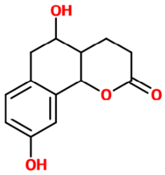
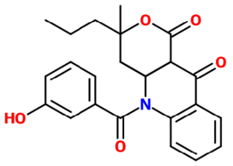
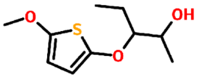
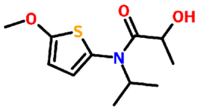
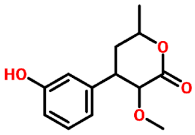
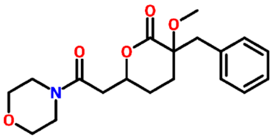
The figure shows a structures with a developed system of cycles, structures with limited mobility, structures with a primary amino group, structures with a special decrease in affinity, as well as structures based on physiologically active alcohols:



Negative properties such as strong narcotic action, high lethality, extrapyramidal side effects, ease of illegal production or cultivation are characteristic features of most potent opiates. But not all structures have the above-mentioned side effects, probably, using more sophisticated strategies of rational drug design, it is possible to combine most of the positive characteristics into one structure, minimizing the common disadvantages of opioid analgesics.

In some cases, it may even be possible to develop a water-insoluble substance that is completely unsuitable for intravenous injection, which could significantly reduce the risk of overdose and infection. Most opioid analgesics were developed 50 years ago, and as drug design capabilities and safety requirements changed, new drugs were needed, and this paper provides examples of possible complex design strategies for new opioid analgesics.

## Condensed structures like hypericin (Hypericum perforatum), but pro-serotonin in nature. Potentially as antidepressants.

Hypericin (Hypericum perforatum) is close to the structure of dopamine. The following structures remain condensed, have the nature of hypericin, but are pro-indole structures.

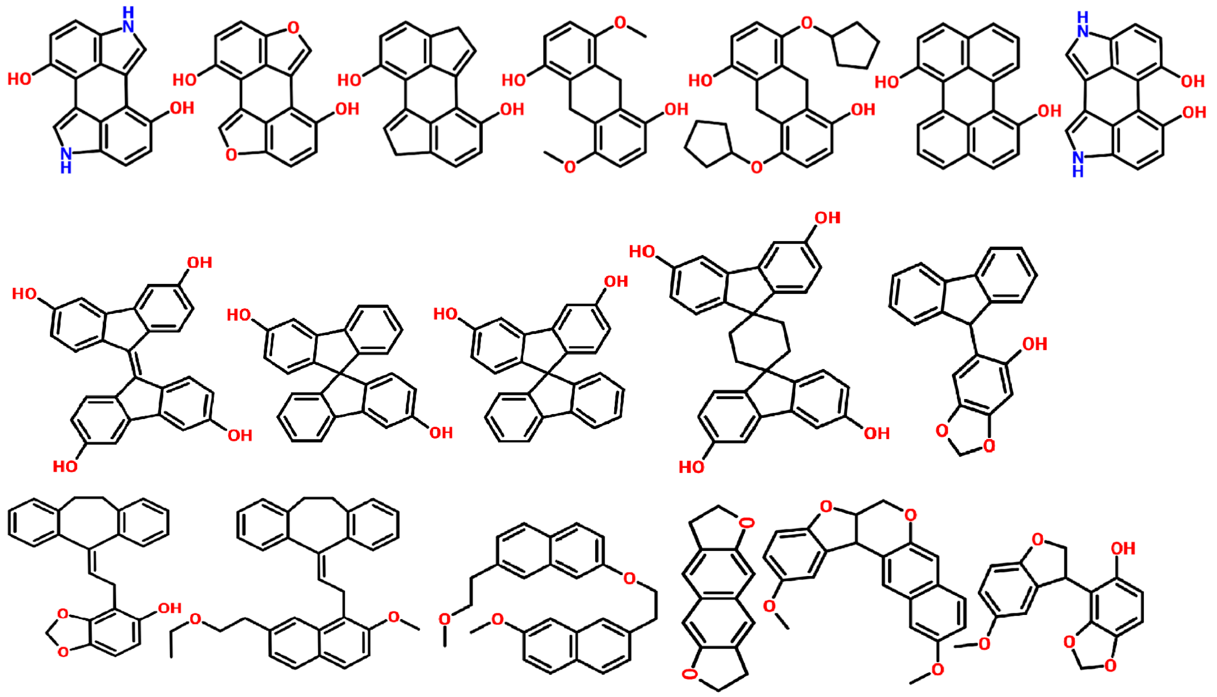
Given the arrangement of serotonin radicals, the structures show variations on the theme of the serotonin molecule and / or its catabolites, in the form of bioinert and entangled condensed nuclei.

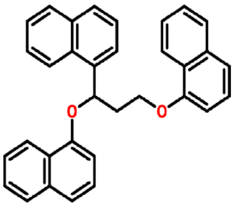
Hypericin is a relatively effective and highly active antidepressant, which is not unimportant, and shows a unique pharmacological profile, where such properties as MAO inhibition, reuptake inhibition, as well as inhibition of catecholamine catabolism, possible regulation of receptor activity and in some cases partial direct mimetic action.

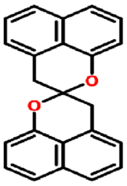
Serotonergic antidepressants are an important part of the therapy for depression, much more represented than dopaminergics, respectively, such structures can be in demand on the pharmacological market, given the great potential regarding the biostability and bioavailability of such structures, and as a consequence, high activity.

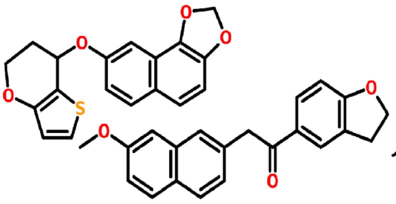
Also presented is a structure in the form of inert compounds, dioxolane and alcohols, some of which may have a direct mimetic effect in the spectrum of the rest of the pharmacology of their action.

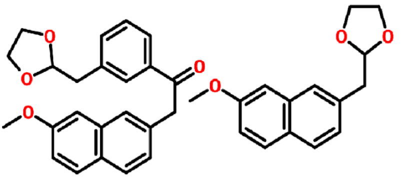
Examples of structures:

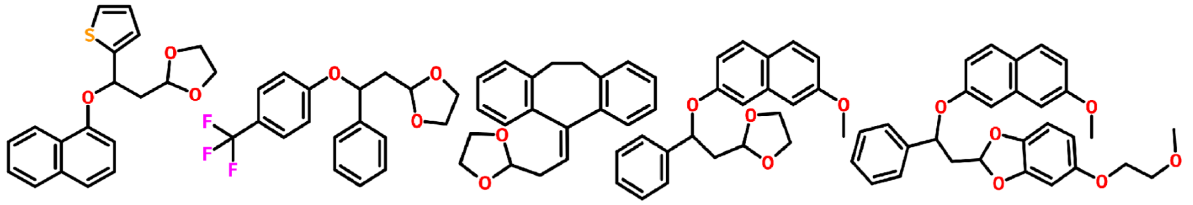


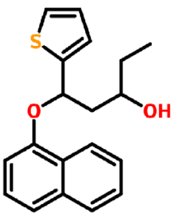


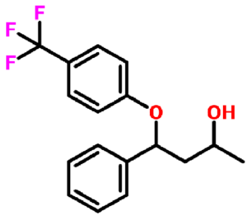












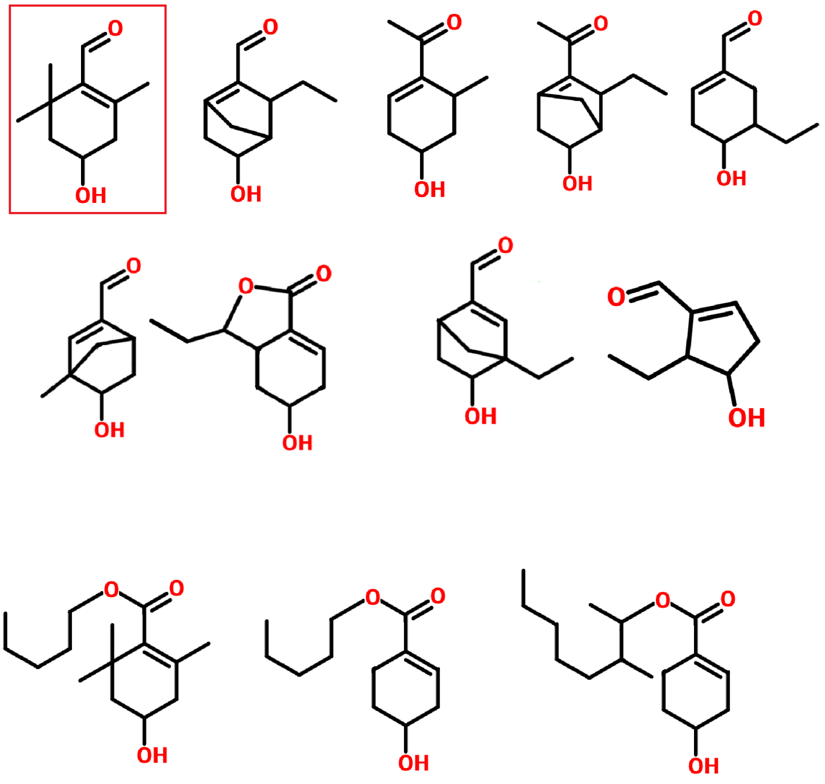
# Dopaminergic and ultra-light cannabinoid terpenes.

Picrocrocin-aglycone from Crocus Sativus (Saffron) has a dose-dependent potential as a dopaminergic and possibly, with some change in radicals in the structure, pro-cannabinoid potential.

In the latter case, a significant role is played by pro-anandamide radicals, such as the methyl (ethyl..) group and hydroxyl group, carboxyl, aldehyde groups, and unsaturated bonds.

Picrocrocin also has a weak pro-glutamate effect, probably caused by the duplicate pro-carboxyl dimethyl radical, which can be replaced by pro cannabinoid groups. A light dopaminergic and cannabinoid is much lighter than marijuana, low marginal effects and a unique combination of qualities of this tandem make such a task not only feasible, but also potentially important for improving the safety of the recreational drug and food market.

Examples of structures:



This work is part of the work aimed at combating hard drugs, creating a more complex and subtle recreational drug market, completely legal and extremely safe. Light drugs have a number of advantages, even when it comes to dose-dependent dopamine reuptake inhibitors, these are always drugs with moderate central effects, even in toxic doses.

Even if we are talking about ultra-light opiates such as alpha terpineol, there is no addiction, tolerance or overdose, because ultra-light mimetics have an extremely low ceiling of maximum activity and are unable to generate a powerful signal at a fundamental, molecular level in any concentration.

Also, such structures are as close as possible to natural terpenes and terpenoids, where between natural structures (picrocrocin-aglycone in the red rectangle) and synthetic derivatives, the difference in the style of structure and the nature of the design of the structure is practically imperceptible. Which gives rise to a new class of compounds: synthetic, physiologically active, pro-native terpenes and terpenoids.

Also, surprisingly, such substances, being lipophilic, are able to turn a barrel of water into a saturated solution of essential oil, this makes them active in small doses, and such substances have the potential to act from a minimum threshold of sensitivity, unlike heavy drugs, which manifest themselves only in strong doses. Such unique properties of ultra-light drugs in the future have a potential much greater than marijuana, since they can legality claim to be safe and easy to use around the world.

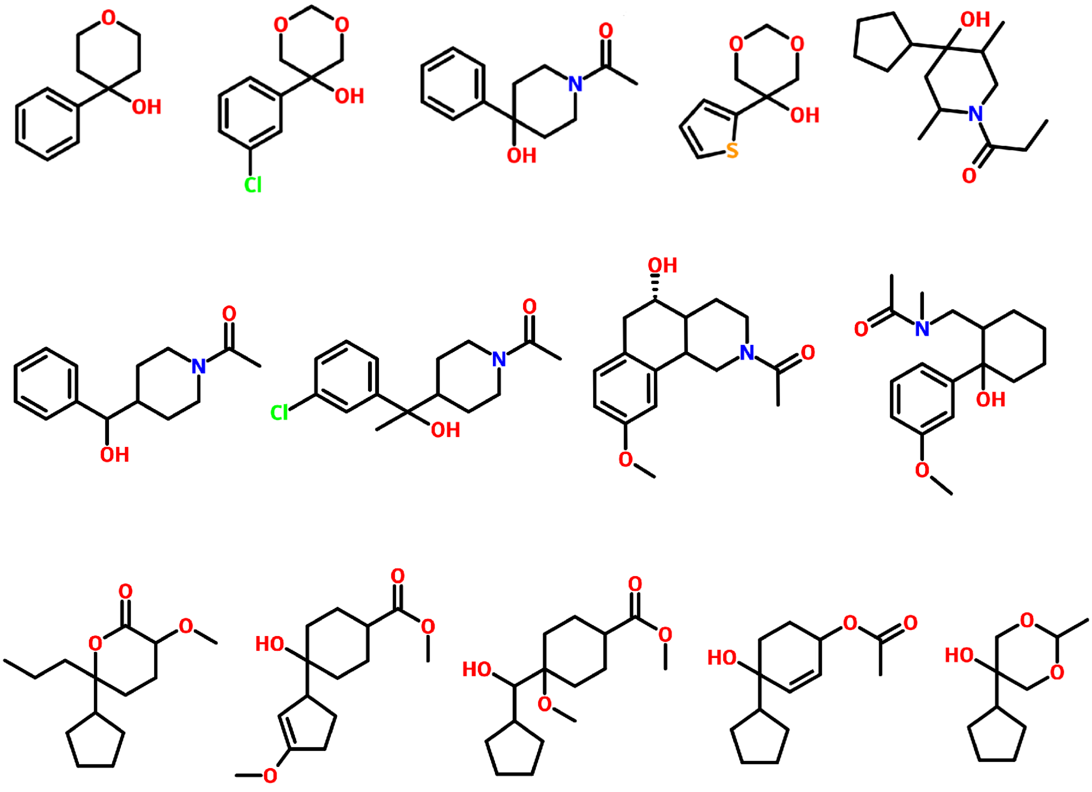
# Examples of drug-design, pharmacological analogs Salvinorin A.

A dissociative agent, such as salvinorin A has a number of limitations for use in research. Salvinorin contains many ester groups. Lactona group vulnerable. The methyl group greatly raises the activity of the drug. Catabolism of the drug is too complicated. Catabolism too fast. Traces of the drug are very small.

Salvinorin is difficult to dosing. Salvinorin is expensive in pure form.

It would be logical to offer a few kernels of pharmacological character with a familiar profile design and catabolism.

Drugs with intelligently placed accents, similar to natural "kappa-peptides" and a good structure design, taking into account the specifics of alcohol:



Simple synthesis, subtle effects, reduced toxicity and lethality, low ceiling of maximum activity, all this may be characteristic of low-affinity pro-terpene kappa opiates, which may give them advantages over ketamine and possibly amantadine. The assumption about the possibility of the existence of such structures was made by the author in the distant 2004, the analysis of structures from lettuce, salvia divinorum and some other varieties, menthol and pharmacological kappa opioids, testifies in favor of the prospects of using rational drug design in the search for subtle, convenient, non-toxic and competitive derivatives

# GABA active synthetic terpenes.

Drugs that enhance the effects of gamma-aminobutyric acid have great pharmacological significance, unlike drugs that enhance the activity of the brain's glutamic system.

But among natural plant physiologically active substances, terpenes, alkaloids, anthocyanins and others, there are extremely few expressed GABA-ergics, these are some compounds in green tea, probably Ivan tea, some anthocyanins, and partly possibly kavalactones. At the same time, glutamate system stimulants are quite widely represented, such as thujone and picrocrocin, active ingredients of wormwood and saffron, nepetalactone and some other lactones.

Glutaminergic natural lactones are often quite active, which cannot be said about GABA-ergic lactones. It is worth noting that lipophilic terpenes can often be highly active and can be candidates for the role of pharmacological agents, if the proper pharmacological profile is provided, the structure includes correct pharmacodynamics, catabolism and other necessary indicators.

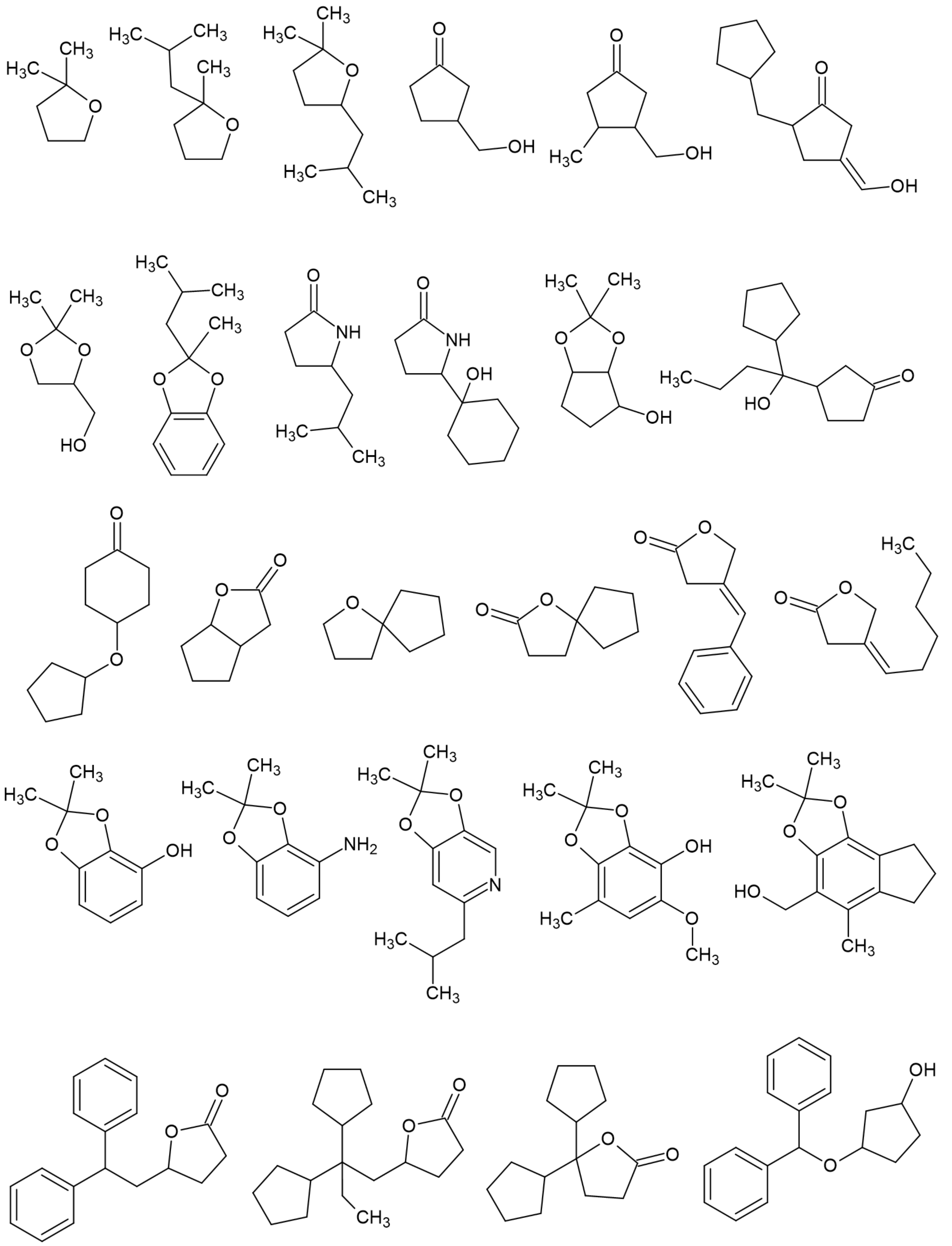
Terpenes, as a rule, have higher activity with structural simplicity, as well as a low activity ceiling and low activity start, which can be an ideal candidate for the role of a light GABA-ergic. And given the high pharmacological significance of GABA drugs, as well as the great interest from research institutes and programs, it would be logical to work with terpenes in this direction, especially since most other types of compounds have already been tested for the role of nootropics, tranquilizers, antipsychotics and sedatives.

This work is somewhat complicated by the simplicity of the structure of GABA and gamma-butyrolactone, as well as their proximity to glutamic acid. In fact, natural pro glutamine terpenes are minimally present in nature precisely because of the high probability of the glutamine system reacting to such derivatives, if they are abundant in pro-carboxyl radicals (carboxyls, keto-gupps, lactones, quaternary carbon atoms). Also, the combination of pro-GABA radicals with pro-opioid radicals is an extremely rare phenomenon for natural terpenoids, and this, in turn, does not allow more powerful antipsychotic potentials among natural substances to be realized.

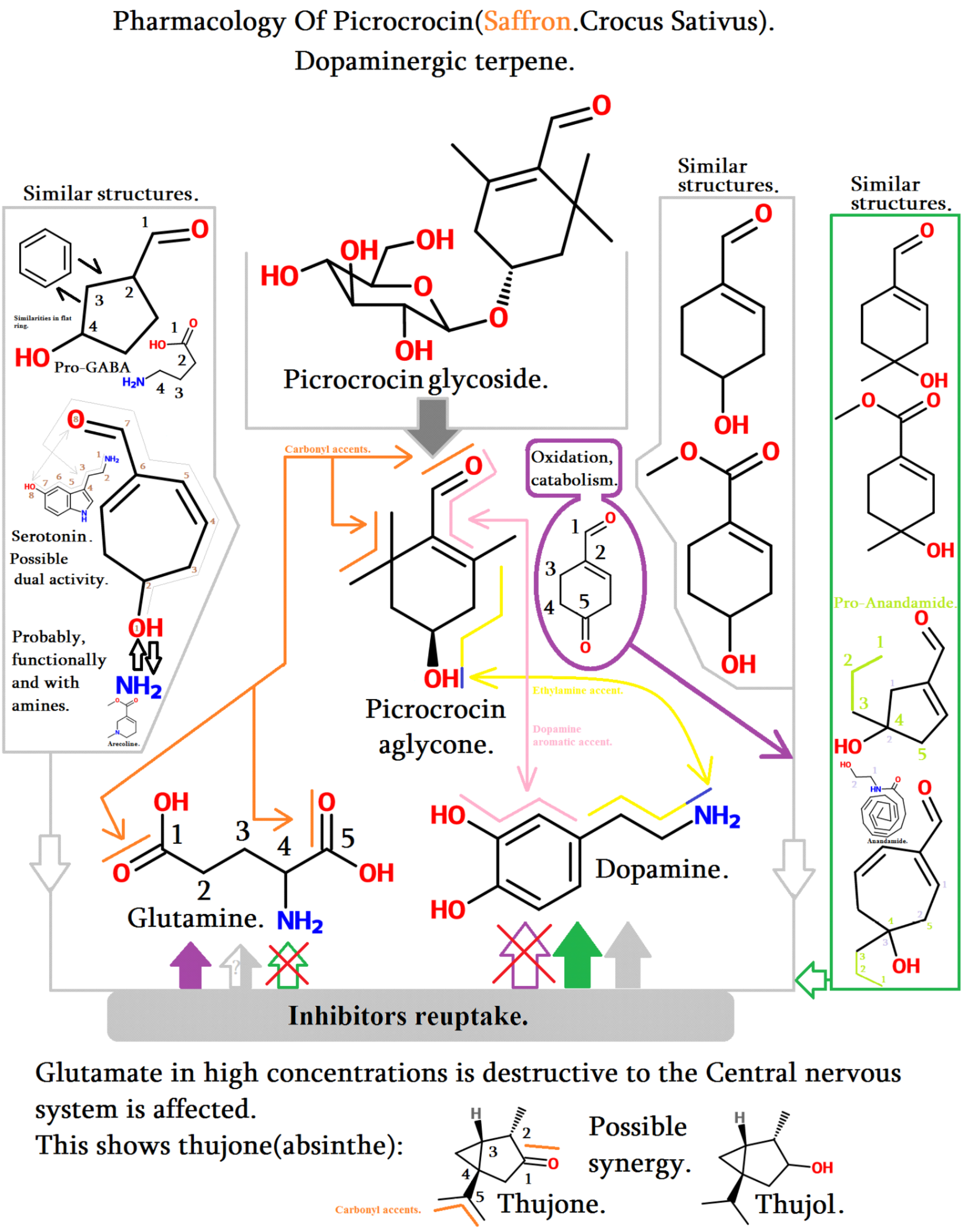
Thus, the way out of this situation may be the use of rational drug design and the development of new strategies in the design of terpenes, the development of semi-synthetic and synthetic terpenes, terpenoids, esters, alcohols, lactones, amides and many other particular examples of small molecule design. Rational design in this case is based on obtaining a structure with an emphasis on one carbonyl group, the necessary distances between the main radicals, new accents and nuclei, dynamic behavior of the molecule and other key points corresponding to GABA or gamma-butyrolactone, as well as heavier pro-GABA derivatives.

Also, such structures can have an effect on pro-opioid clusters within GABA receptors, as well as a direct mimetic kappa and mu opioid effect. With the inclusion of special radicals, it is also possible to realize pro-cannabinoid activity, which is demonstrated by some structures. The spectrum of qualitative and quantitative effects of active GABA drugs can thus be significantly expanded.

The figure shows some candidates for the role of GABA-active synthetic terpenes of different groups and design strategies:



Hypothetical scheme of the pharmacology of Picrocrocin (Saffron. Crocus Sativus) and structures similar to picrocrocin.

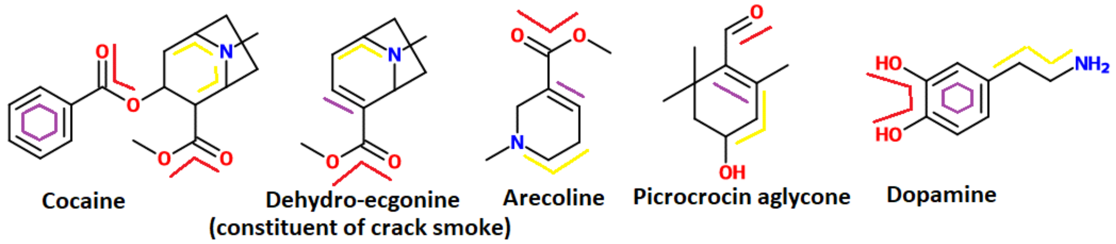


Pharmacology Of Picrocrocin(Saffron.Crocus Sativus).
Dopaminergic terpene.

Glutamate in high concentrations is destructive to the Central nervous system is affected.
This shows thujone(absinthe):

Similar structures.
Similarities in flat ring.
Pro-GABA
Serotonin.
Possible dual activity.
Probably, functionally and with amines.
Arecoline.
Picrocrocin glycoside.
Carbonyl accents.
Oxidation, catabolism.
Picrocrocin aglycone.
Ethylamine accent.
Dopamine aromatic accent.
Similar structures.
Similar structures.
Pro-Anandamide.
Anandamide.
Glutamine.
Dopamine.
Inhibitors reuptake.
Possible synergy.
Thujone.
Thujol.
Carbonyl accents.

Comparison of the structures of natural alkaloids



The scheme shows dopaminergic terpenes and possible synthetic variations with a different nature of pharmacological action.

The scheme is made in a non-strict style, using a variety of colors and scales. For ease of display of information, graphic symbols are used in the scheme showing interatomic distances in structures, complementary elements of structures. The figure also shows the structure of the corresponding neurotransmitters. Examples of complementary substances and logical paths, hints and answers regarding the pharmacology of picrocrocin in a narrow and extremely broad sense.

The scheme shows possible ways of reaction of the glutamine and dopamine systems of the brain to picrocrocin. Such as the presence or absence of direct mimetic effect, the presence or absence of inhibition of the reuptake of neurotransmitters, etc.

Possible ways of acquiring other properties are also indicated using thujone and picrocrocin-like structures as examples. The work shows possible causes of picrocrocin glutamate activity and possible solutions to this drawback. The article also presents structures that claim to be complex physiologically active substances with a new set of characteristics, including affinity for GABA, serotonin, and anandamide.

References:

Journal of Behavioral and Brain Science, 2013, 3, 315-319. Aqueous Extract of Saffron (Crocus sativus) Increases Brain Dopamine and Glutamate Concentrations in Rats. Hosseinali Ettehadi. Seyedeh Nargesolsadat Mojabi. Mina Ranjbaran. Jamal Shams. Hedayat Sahraei. Mahdi Hedayati. Farzad Asefi. http://file.scirp.org/pdf/JBBS_2013071810240060.pdf

Physiologically active alcohols, analgesics and dopaminergic. Yaroslav Zaitsev. Academia.edu. https://www.academia.edu/26483613/Possible_new_vector_drug_design._Physiologically_active_alcohols_analgesics_and_dopaminergic.odt

Dopaminergic and superlight cannabinoid terpenes. https://www.academia.edu/26367905/Possible_new_vector_drug_design._Dopaminergic_and_superlight_cannabinoid_terpenes

Structures close to reuptake inhibitors neurotransmitters and serotonin. https://www.academia.edu/30615265/Structures_close_to_reuptake_inhibitors_neurotransmitters_and_seroto nin

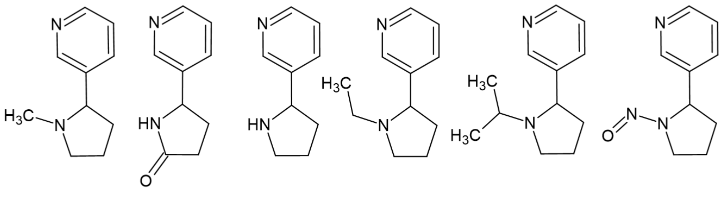
GABA active synthetic terpenes. https://www.academia.edu/29523872/GABA_active_synthetic_terpenes

Synthetic terpenes as a universal GABAergic, dopaminergic and light cannabinoids.https://www.academia.edu/29544735/Synthetic_terpenes_as_a_universal_GABAergic_dopaminergic_and_li ght_cannabinoids

Superlight synthetic cannabinoids. https://www.academia.edu/26201468/Possible_new_vector_drug_design._Superlight_synthetic_cannabinoid

# Nicotine as dopaminergic.

Examples are derivatives of nicotine, search structures with low toxicity and carcinogenicity.



Nicotine, cotinine, nornicotine, ethylnicotine, isopropyl nicotine, nitrosonicotine.

Nicotine has a number of structural and pharmacological disadvantages, and it is difficult to model more acceptable structures based on nicotine, and there have been virtually no such precedents. However, the pharmacology of nicotine can be rethought and modernized by changing its structure.

The negative aspects of nicotine, such as the vasoconstrictor effect and high toxicity, are associated with the effect on the sympathetic nervous system through the release of dopamine and adrenaline and the toxic effects inherent in acetylcholine hyperstimulation. The carcinogenic effects of nicotine are most likely associated with the nitrosamines of nornicotine and the pyrolysis products in the smoke. Pure nicotine is slightly carcinogenic, but as a rule, nitrosamines of low-carcinogenic and moderately carcinogenic amines are highly carcinogenic. Natural raw materials contain nitrosamines, respectively, are more dangerous, but only on one point, let's consider the rest.

Minor components and modification of recreational qualities of tobacco products. Tobacco contains minor alkaloids, these are cotinine, nornicotine, ethylnicotine, isopropylnicotine. Cotinine is possibly responsible for the high recreational effects of cigars, since it is better absorbed from the oral cavity compared to nicotine, and a large cigar with many years of aging contains relatively much cotinine. Cotinine also has an antidepressant effect and is considered as a candidate for the role of an antidepressant. Nornicotine is a precursor of nitrosamine nicotine, and isopropyl nicotine can have side effects with a strong effect on the sympathetic system.

The main pharmacological motives that reduce toxicity and side effects, but preserve the recreational qualities of nicotine are the dopaminergic potential of the central effects. The conditional balance between the acetylcholine component and the pro-dopamine effect can reduce acetylcholine toxicity and increase the qualitative effects. Also, nornicotine, isopropylamine and ethylnicotine are probably unsuitable minor impurities.

How to reduce toxicity and increase dopaminergic properties, for example, it is possible to create an optimal nicotine/cotinine ratio that does not contain nitrosamines, nornicotine and other dangerous impurities.

Which nicotine derivatives can have reduced toxicity and increased recreational qualities. Is it possible to rationally come to new nicotine derivatives, does the structure of nicotine provide an answer to this question upon detailed consideration. It is possible that yes, in some readings, nicotine is similar to the structure of phenethylamine, but as if turned inside out, where the cyclopentane ring mimics the aromatic ring, and the aromatic ring is similar to the ethylamine group.

This view of nicotine does not contradict the classical ideas about nicotine as a substance close to acetylcholine, rather it can complement the basic pharmacological scheme. Indeed, in the structure of nicotine there are no fewer radicals close to phenethylamine than radicals close to acetylcholine, but the phenethylamine component in it can be much more complex and manifest itself not in static behavior but in the dynamic movement of the molecule on the surface of the target.

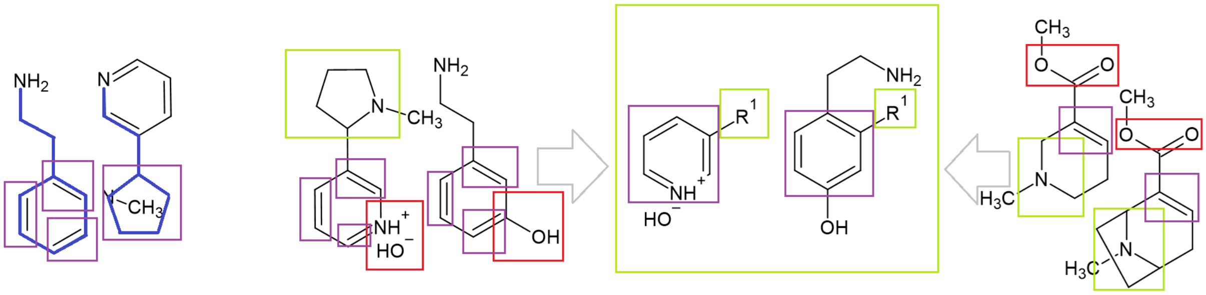
Let's describe the theoretical part and add a diagram. So nicotine, its aliphatic part (pyrrolidine), is similar to the benzyl radical benzylamine since it is separated from the aromatic ring by only one carbon atom, but pyrrolidine itself is similar to a flat five-membered chain and can mimic the aromatic ring. Also, in some cases, benzylamine variants can be active as phenethylamines, for example, arecoline, or crack smoke containing dehydrogenated ecgonine, can have activity as dopamine reuptake inhibitors, although between the double bond and the amino group there is only one carbon atom, mimicking benzylamine. Further, the aromatic ring (pyridine) can mimic the aromatic ring of benzene, but it can also be similar to ethylamine since it contains an ethylamine group inscribed in the aromatic ring, unsaturated and flat, but nevertheless, it is a pro-ethylamine fragment. In dynamics, such a molecule can play the role of norepinephrine or dopamine, or rather dopamine, since there is no hydroxyl group next to the amino group.

And so there are several options for reading nicotine as dopamine:

1. The pyrrolidone group is pro-benzene, and pyridine plays the role of pro-ethylamine.

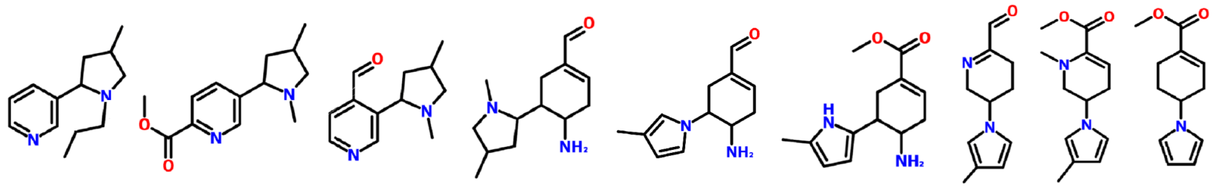
2. Pyrrolidine, being a benzyl radical, mimics phenethylamine in the cis position, then the amino group of pyridine becomes para-position.

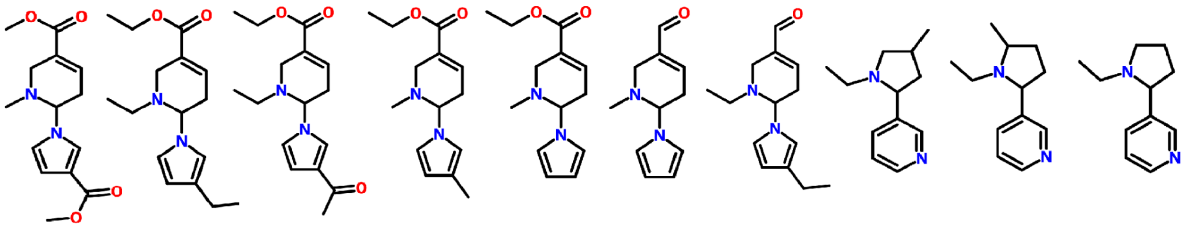
3. Dynamic transitions between different readings, creating a complex mimetic pro-dopamine picture:

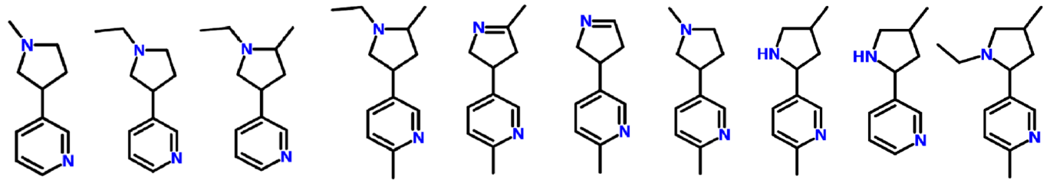


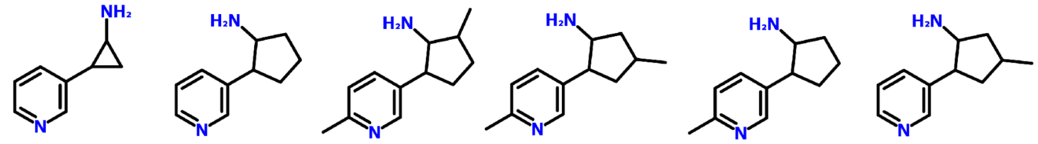
Pharmacological scheme of dopaminergic potential of nicotine, principle, third-party examples - arecoline methyl ecgonidine(AEME).

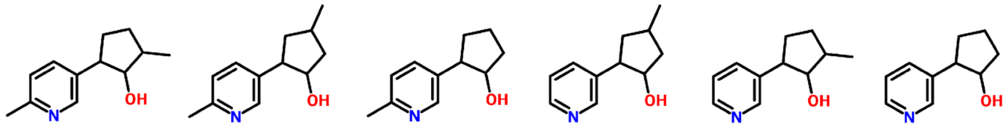
What changes in the structure of nicotine can claim reduced toxicity and an improved pharmacological profile in the context of this work? Could it be substituents in the amino group of pyrrolidine, probably yes, it can be a propyl and even butyl radical, perhaps such a move will reduce the sympathetic effects and give the structure more relaxation, maybe even with subtle pro-opioid notes (the propyl group can also be next to the amino group). Could it be a methyl radical in pyridine and pyrrolidine? Yes, such a radical can mimic the aromatic hydroxyl of dopamine, turning nicotine into a pronounced dopaminergic. Could it be an ester group, yes, an aldehyde yes, can such derivatives not be carcinogenic, yes, this is also possible. Is it possible to get away from the nicotine core and create similar structures, but of a completely different nature, probably yes, examples of structures:

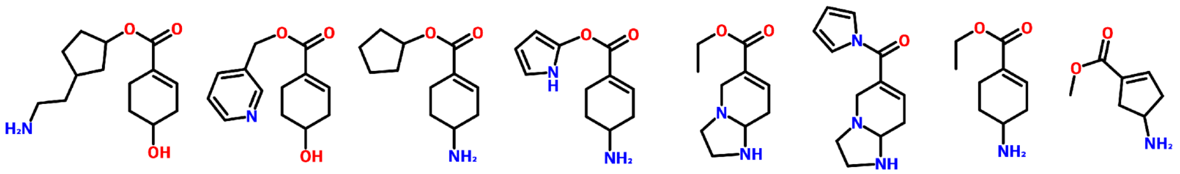


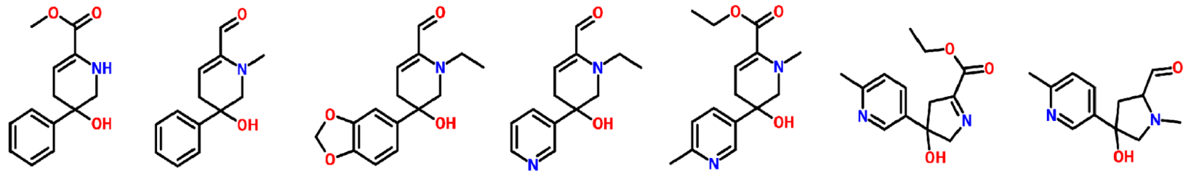


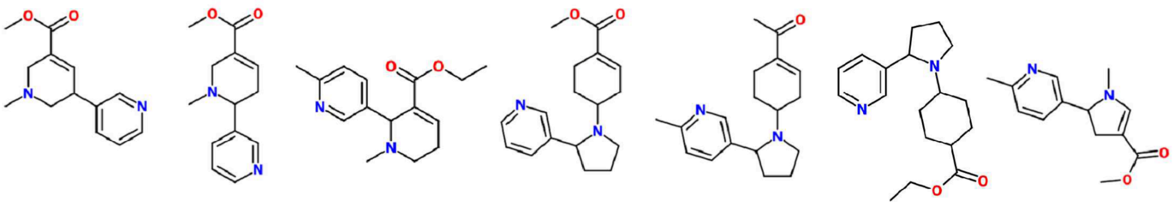












So, nicotine is not carcinogenic, low-toxicity, highly recreational and has minimal side effects, with minimal dependence, is it possible? Probably yes, nicotine dependence is caused by a sharp increase in nicotine concentration when inhaling cigarette smoke, for example, cigars are capable of causing less dependence, although their recreational properties are much higher. Recreational properties are not always associated with dependence, nicotine derivatives are not required to be carcinogens, especially with more advanced delivery methods, such as the ultrasound method of delivery. Nicotine can both constrict and dilate blood vessels, especially since nicotine derivatives, which have a much wider range of possible effects, can fit into the safety limits regarding the narrowing of peripheral blood vessels.

# Peripheral opioids and cannabinoids, local analgesics.

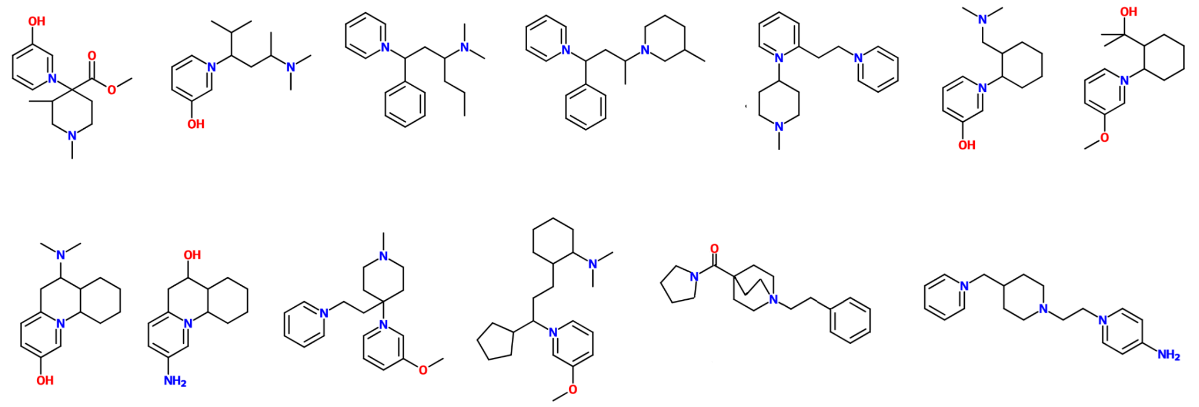
It is known that cannabinoids and opioids have a central analgesic effect. It is also known that they are active when applied locally. For example, marijuana-based ointments, as well as ointments based on rapidly degrading endogenous endorphins and enkephalins.

Such drugs have antinociceptive potential in inflammatory processes, chronic pain or injuries.

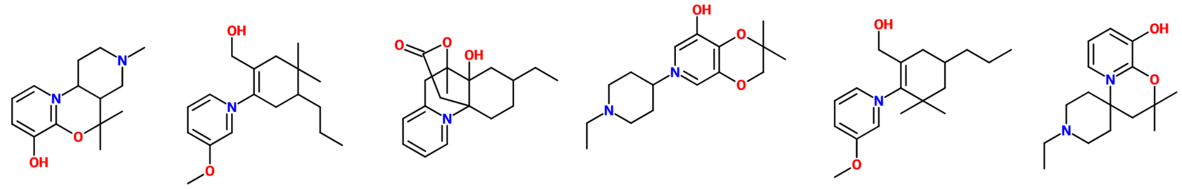
This paper proposes to consider in more detail the possibilities of rational drug design of peripheral analgesics that do not pass the blood-brain barrier, using quaternary ammonium base derivatives as an example.

Local application provides reduced toxicity and the absence of side effects characteristic of opiates, such as tolerance and addiction, and also eliminates the narcotic effect.

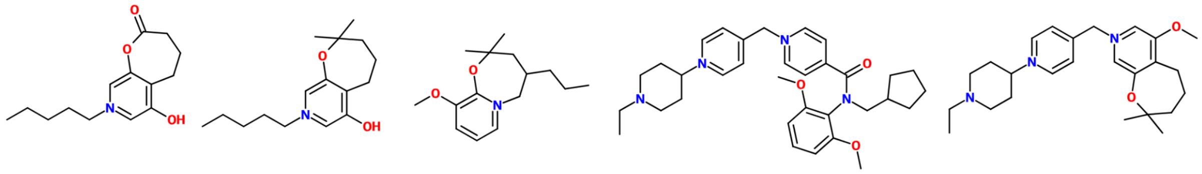
The presented structures of cannabinoids and opiates have a reduced ability to penetrate biological barriers due to the inclusion of quaternary ammonium bases in the structure. The diagram shows both cannabinoids and opiates, as well as substances with a universal structure, which have the ability to be active in two directions at once:



Peripheral opioids.



Pro-opioid and cannabinoid combined structures.



Cannabinoid structures.

# Opioid radicals in the structure of antipsychotics, anxiolytics, anticonvulsants and some others. What big pharma is hiding.

Let's ask a few important questions that have no answers yet, questions that no one has dared to ask, questions that could greatly undermine the reputation of pharmaceutical giants, change the rules for registering pharmaceutical drugs, revise drug access lists and much more.

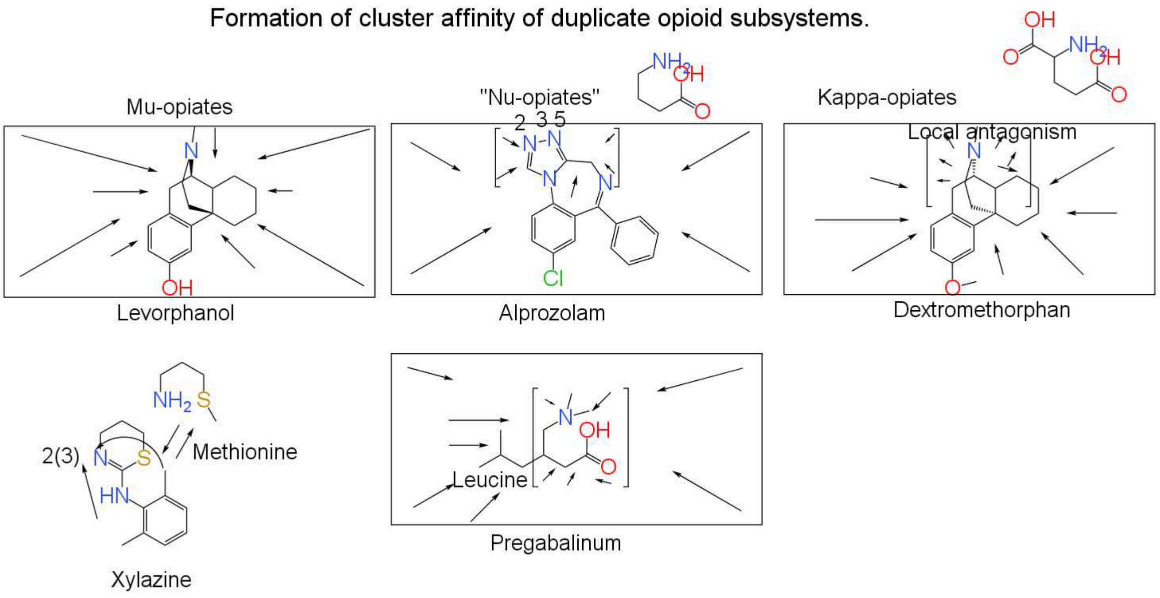
Neuroleptics, anxiolytics, some anticonvulsants and tranquilizers have radicals in their structure that are characteristic of direct opioid mimetics.

These are radicals characteristic of meth and leu enkephalins - aromatic nuclei, an amino group at a distance of 2, 3, 5 carbon bonds from the aromatic nucleus, cyclic saturated or hetero chemical inclusions, fragments of leucine or methionine (or their pharmacological analogues). All these radicals, when correctly placed, are capable of causing a powerful affinity for opioid receptors.

Some drugs have a slightly less pronounced similarity to the opioid structure, while others are closer to enkephalins and opiates in structure.

The drugs that are closest, in my opinion, in structure to opiates are Xanax, Pregabalin, Coaxil and Xylazine.

Let's analyze the chemical structure of these drugs and determine, if possible, what differences they have from similar analogs, but with a less dubious history.


Formation of cluster affinity of duplicate opioid subsystems.
Mu-opiates
N
OH
Levorphanol
"Nu-opiates"
2 3 5
N-N
N
N
NH2
OH
O
Cl
Alprozolam
Kappa-opiates
Local antagonism
OH
O
NH2
OH
O
N
O
Dextromethorphan
NH2
S
Methionine
2(3)
N
S
HN
Xylazine
N
OH
O
Leucine
Pregabalinum

Alprazolam (Xanax), unlike most drugs of the benzodiazepine series, has a characteristic, additional hetero-chemical ring. With respect to pro-opioid radicals, the structure of Alprazolam is rich in them, and is also rich in correct relationships between radicals, such as:

Two aromatic nuclei are located at a distance of one carbon (methadone scheme of arrangement of aromatic nuclei), the methadone scheme is well implemented by means of an additional pentagonal cycle with two amino groups.

Amino groups are removed from the aromatic nucleus both at a distance of two carbon atoms, and at three and five, which fully corresponds to opioids. In addition to a small but significant feature, the above two additional amino groups are part of an unsaturated cycle and are partially aromatized. This nature of amino groups can reduce affinity for mu-opioid receptors, but maintain affinity for other receptors, for example, the pro-opioid cluster included in the structure of the GABA receptor.

GABA receptor and opiates? It is impossible, it is fiction or... It is high time to move on to the second part of the investigation. As is known, there are drugs with kappa opioid activity, some of these drugs are like two peas in a pod with known opiates, they are distinguished almost only by isomerism, for example, levorphanol is an opiate 5 times more powerful than heroin, and dextromethorphan is a kappa opiate, which is almost identical in structure, but exhibits affinity for completely different receptors.

These receptors are not officially part of the opioid signaling system, because this is an NMDA receptor, and glutamate has never been an opiate.

What's the catch?

I will express my point of view, nothing more, glutamate is an amino acid, it is similar to a fragment of enkephalin, to the central fragment of enkephalin, like GABA, it is the internal salt of enkephalins, in fact, it is a fragment close to GABA or glutamate. All benzodiazepine drugs, some gamk-ergic drugs, most antipsychotics and many tranquilizers contain in their structure both a group of atoms corresponding to the GABA molecule and a continuation in the form of pro-opioid radicals. This is necessary so that the drug molecule is sorbed on a wider area, because the GABA receptor is a dual receptor, behind the cluster recognizing GABA there is a wider field recognizing opioid radicals.

This is exactly how kappa opiates work, as you know, they are antagonists of NMDA receptors, which is logical, because they do not have radicals similar to glutamate. To be honest, they should not attach to the NMDA receptor at all, but they are helped by proendorphin radicals, they provide high affinity. And so, when dextromethorphan attaches to the NMDA receptor, it blocks it, which is what should have happened.

Yes, the blockade occurs because the opioid cluster of the NMDA receptor holds dextromethorphan, which ultimately blocks the path for glutamate. But what gives this unique effect of kappa opiates? It is not glutamate or its absence, it is the narrowing of the opioid cluster around the NMDA receptor. It is this signal that is so different from the standard role of glutamate, because it is a duplicate opioid system. A duplicate opioid system, evolutionarily combined with such neurotransmitters as glutamate and GABA.

And if for a powerful sedative effect the presence of minimal opioid radicals of benzodiazepines is enough. In this case the dosage of the drug will be higher, the pro-opioid the effect will be less, the sedation will be greater. Then in the case of more pro-opioid radicals, the dosage becomes lower, the sedation is not so pronounced, the value on the white-gray-black market grows to the skies as does the withdrawal syndrome, the structure reflects the essence of the drug.

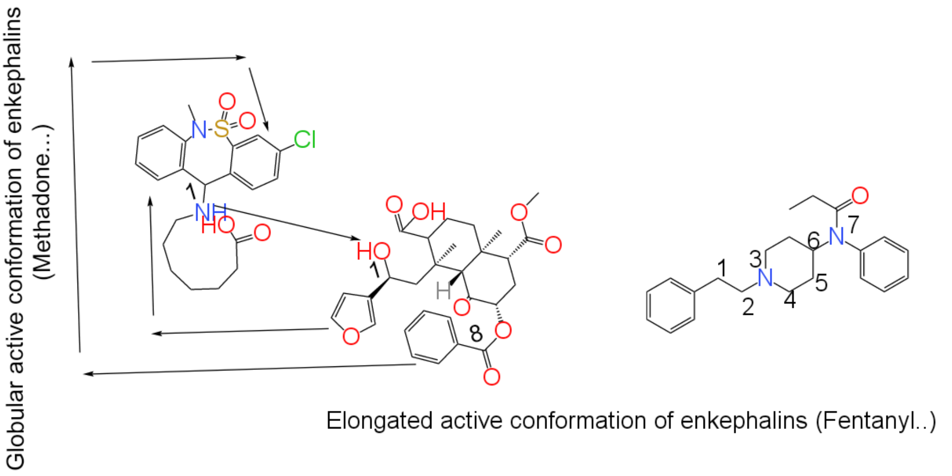
But what can we say about Pregabalin then, since it is essentially GABA with a small tail, almost like GABA. No, absolutely not, and here's why: GABA is a spatial fragment of enkephalins, it is the internal salt of enkephalins when enkephalin is in an active configuration. The "small radical" near GABA is a fragment of leucine, it is in the correct position for enkephalin and is able to collect half of the enkephalin receptor.

This is possible because the amino group of enkephalins and the radicals of the terminal amino acid of enkephalins, such as the leucine tail, carboxyl group or methionine tail, are not rigidly bound in enkephalins. But pregabalin contains a pro-leucine tail linked to the amino group by a carbon bond. This technique allows even a small molecule to collapse the enkephalin receptor onto itself and gives a signal. Similar techniques were used in the development of methadone, 14-methoxymetopon, etorphine and fentanyls. Such a technique can work even with minimal structural mass, even menthol can have a small kappa activity, due to the ring, hydroxyl and leucine radical.

As for Coaxil, Tianeptine as an effective antidepressant may be partly due to its pro-opioid action, opium tincture is one of the first known antidepressants, and seriously, the pro-opioid action in this case can improve both the result and sales. Tianeptine contains a pro-methadone aromatic ring and an amino group in the first position relative to them, which is not typical of opiates. More precisely, it is not typical of opiates, but with one aromatic group, for example, the powerful opioid Herkinorin, which has two aromatic groups, contains a hydroxyl (functioning instead of an amino group), in the first position near the aromatic ring of furan. In this case, as in the case of Pregabalin, an internal salt is formed with a carboxyl group, which is enhanced by a powerful methadone group, which attracts the receptor.

Moreover, in the opposite position from the amino group, in the structure of Coaxil there is a large sulfur-containing radical and a number of other bulky radicals that are capable of pushing the aromatic nucleus out of its position relative to the receptor and shifting the amino group to the second or third position, as is the case with mescaline derivatives or mephedrone, similar techniques are also often used in pharmacology.

Tianeptine, Herkinorin and Phentanile, different structures with similar radicals and specific proximity.


Globular active conformation of enkephalins
(Methadone...)
O
N-S=O
Cl
1
NH
HO
O
O OH
O
O
HO
1
H
O
8
O
O
O
7
N
6
3
1
N
2
4
5
Elongated active conformation of enkephalins (Fentanyl..)

Xylazine is used to enhance the opioid effect of opiates, one of a number of unremarkable drugs, opioid notes in which are not many, no more than in Alpha-PVP.

Alpha-PVP, among other things, is a pharmacological fragment of enkephalin (including this explains the pleasant relaxation at the beginning of the effect, as well as addiction similar to opioid), the phenethylamine group of PVP is responsible for the tyrosine fragment, the cycle enhances opioid notes, and the butyl tail as in etorphine or 14-methoxymetopon or butanol or methadone, all these are opiates or drugs for anesthesia (butanol), such radicals completely open the core in the opioid reading.

Xylazine has a cyclic structure, this is certainly not enough, its simplest structure includes sulfur, when the methylated aromatic nucleus rotates around its axis, one of the methyls becomes opposite the sulfur, this combination can be extremely similar to the tail of methionine in enkephalins. Accordingly, like met-enkephalin, such a structure can promote powerful met-enkephalin relaxation in a mixture with opiates. This is a met-enkephalin booster, modulating the composition of opiates towards extreme relaxation and decreased activity.

So, it is likely that the opioid notes in the structures of neuroleptics, antipsychotics and other pharmacological groups - this is not a rare phenomenon. It is also likely that the correlation between specific radicals and potential value on the gray market can be determined with some sufficient accuracy.

Also, the presence of duplicate opioid systems can explain many cases of pro-opioid effects of drugs, in the absence of a clear mechanism that could describe such manifestations.

How many duplicate opioid neural systems exist besides glutamate and GABA? If evolutionarily monomeric neurotransmitters - catecholamines, amino acids, butyrolactone, acetylcholine, are much younger than enkephalins. Then it is possible that there are as many duplicate opioid neural receptors as there are all types of neurotransmitters.

In the event that mono-neurotransmitter receptors evolved from enkephalin receptors, since almost each of them resembles a fragment of enkephalin, and by narrowing the area of responsibility, catecholamine and amino acid receptors could have evolved. Then each receptor consists of two conditional clusters, an internal monomeric and an external one that perceives enkephalin radicals.

This is the maximum possible number of double receptors, in addition, the existence of many subtypes of receptors is possible...

To what extent this theory can be verified today is a difficult question and much depends on the vector of efforts and funding of programs. But one thing is known for sure, almost every antipsychotic and related groups of drugs contain pro-opioid notes, often with the correct pro-opioid sequence and with observance of precise distances at the molecular level.

Such multiple coincidences, cascades of coincidences and cascades of mutual intersections of facts cannot be ignored.

The issue under consideration probably requires an unbiased analysis, updating of experimental data, changes in the requirements for the development of drugs, revision of scientific terminology and the level of control over the circulation of drugs.

# Physics lesson for a teacher of physics, history and anthropology.

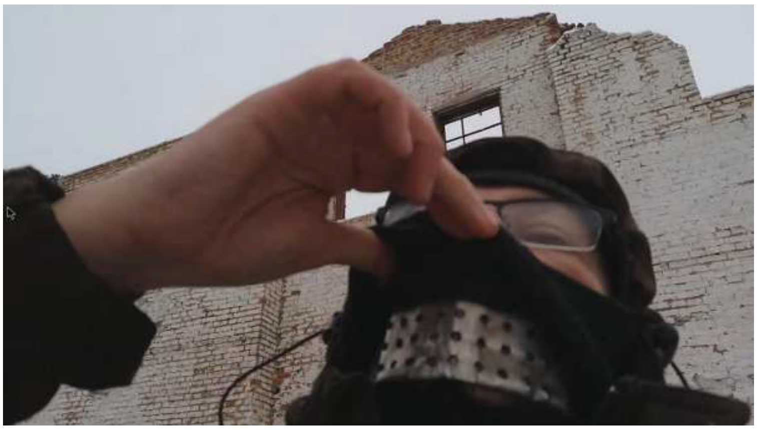
Have you ever wondered what the role of a warm scarf is in a wardrobe? This element of clothing is many thousands of years old, perhaps hundreds of thousands, which may be simpler and brought to its logical conclusion by the experience of our ancestors and modern industry and science.

Yes, this example is not random and all the statements listed here are wrong!

The scarf does not warm the air, it only covers the face and creates a small air buffer that steals oxygen during shallow breathing in winter. The thermal capacity of the scarf is minimal, and is mainly provided by the fabric and settled moisture, which is not enough to absorb much heat from the exhaled air flow.

Perhaps someone has already guessed what I'm getting at, yes, to recover the heat of exhaled air, you need to have more available heat capacity, greater heat capacity and good thermal conductivity - metal, diamond, water..  a heat exchanger.

That's what I did, my prototype has been working for many years and gives me great comfort. It's a scarf between two layers of which an aluminum perforated plate is inserted. This allows me to feel like a snowy winter, even when there is snowfall and blizzard, like in spring or autumn - I can ride my bike with pleasure all day long, without any consequences.



Self-portrait against the backdrop of a destroyed production facility.

Yes, this is a working prototype, I often use my design and experiment on myself, this aluminum plate has been working properly for 4 years, does not require electricity and has no competitors. Yes, with an industrial approach, this can be realized even better, for example, if you sew a scarf with copper thread coated with durable varnish.

Yes, this raises the air temperature significantly, but not to the level of a summer day, of course, but this is enough to not over-cool your lungs and enjoy winter walks or sports, for hours, like in summer, but from the beauty of winter. This protects the mucous membranes of the larynx from hypothermia and cold injury, protects from the initiation of damage by viruses and bacteria, and protects from the reduction of antiviral natural substances during hypothermia...

As a result, you get something that you could not imagine all these many thousands of years.

# Physiologically active alcohols, analgesics and dopaminergics.

Physiologically active alcohols are poorly represented in pharmacology. Rare examples of such natural adaptogens are the active ingredients of Rhodiola rosea, Echinacea, Schisandra, Eleutherococcus, and ginseng root. Also, the antidepressant p-methyl-alpha-beta-tetramethyl-phenylethanol, which has been withdrawn from circulation.

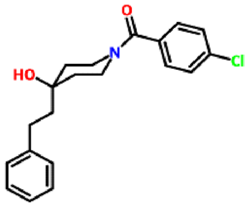
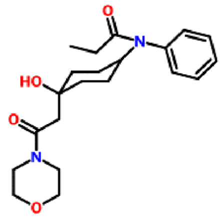
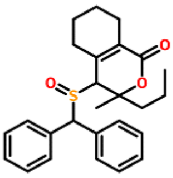
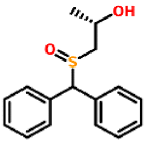
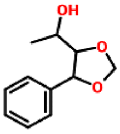
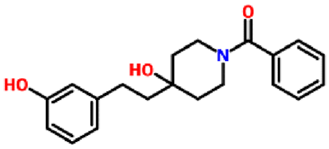
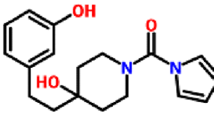
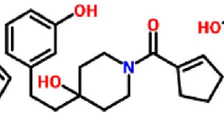
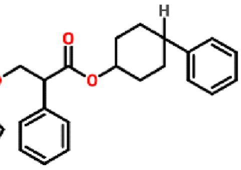
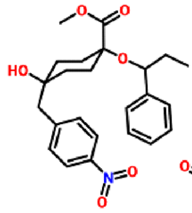
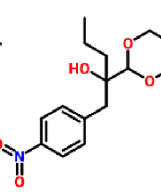
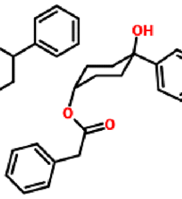
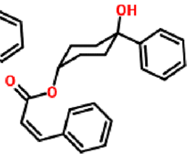
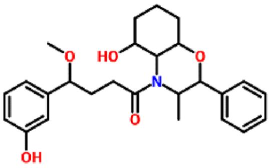
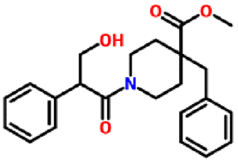
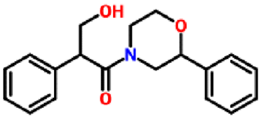
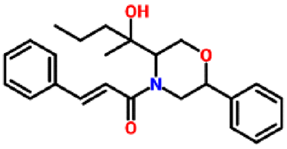
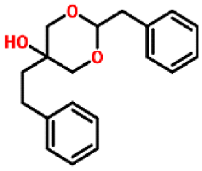
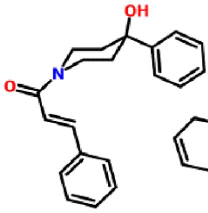
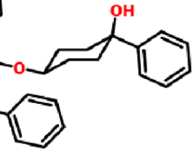
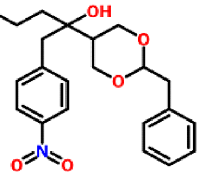
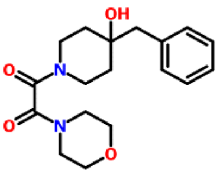
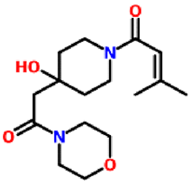
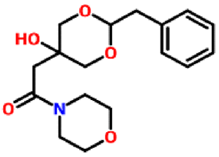
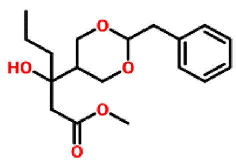
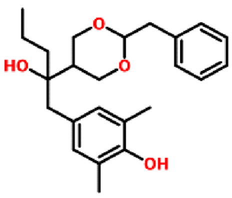
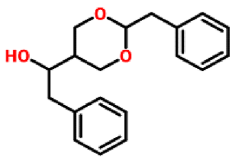
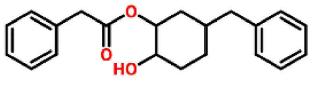
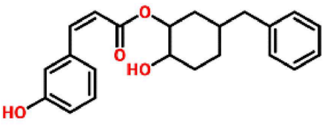
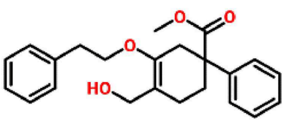
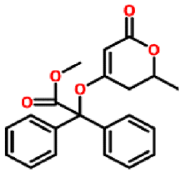
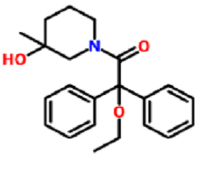
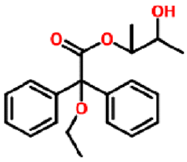
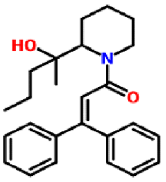
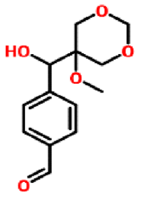
Natural kappa active alcohols are menthol and salvinorin, pharmacologically active terpenoids of agarwood, Salvia Splendens, picrocrocin aglycone from Crocus Sativus flowers, and α-terpineol from Cardamom.

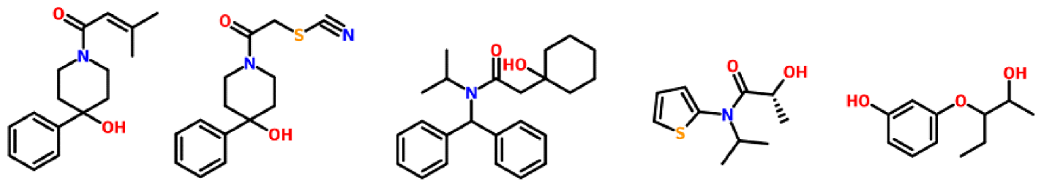
Some of them have a thousand-year tradition, the potential of ginseng, saffron and cardamom, indicate the ability of physiologically active alcohols to provide valuable therapeutic effects and great potential for the development of semi-synthetic and synthetic pro-terpenoid mimetics, modulators and inhibitors of neurotransmitter reuptake. The prospects for using physiologically active ones may be due to their special physicochemical and pharmacological properties. Such as light mimetic properties in relation to the amino group, the alcohol group has much less affinity compared to the amino group when used as a mimetic radical of amino groups. At the same time, the hydroxyl group is much more lipophilic and better passes the blood-brain barrier. Thus, terpenoids with a small molecular weight and even small terpenes are capable of providing a light but noticeable effect, and in insignificant doses, often less than similar amines. Also, such alcohols often have a very low ceiling of maximum activity, for example, α-terpineol from cardamom, being a pro-opioid, it does not cause blocking of the respiratory center, tolerance or dependence. Terpineol and similar light pro-terpene alcohols also have a much lighter effect and a noticeable effect from smaller doses, compared to powerful analgesics, the noticeable effects of which begin at doses of about 1M. The latter means that the therapeutic effects manifest themselves at much lower levels than the noticeable narcotic effects, and the upper limit of activity of such examples may not reach narcotic effects. Thus, alpha terpineol can be an example of a legal, non-lethal, non-narcotic, practically safe pro-opioid terpene (in which the alcohol group plays the role of a mimetic of the amino group of enkephalin - a physiologically active alcohol). Such properties of physiologically active alcohols can provide a whole arsenal of drugs with unique properties, such as ultra-light opiates, and water-insoluble opiates that cannot be used intravenously, and completely new antidepressants and light stimulants, and much more.

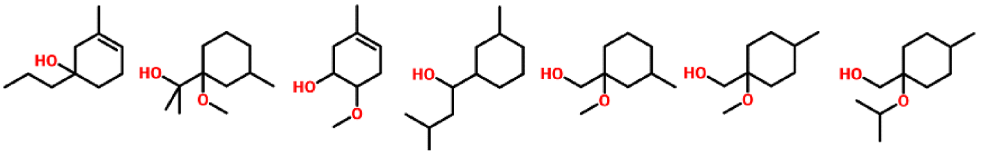
One of the most advantageous positions is ultra-light opiates at a completely new level of safety. Since the safety of opiates is an issue that urgently requires a solution, such drugs could serve as a healthier alternative to existing powerful analgesics with an activity ceiling much higher than the lethal dose.

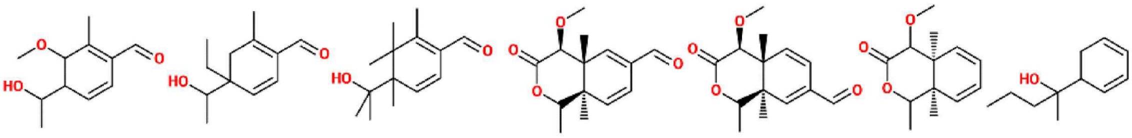
The activity ceiling of some light alcohols can be much lower than the lethal dose, in fact, alcohols can revolutionize the safety of opiates.

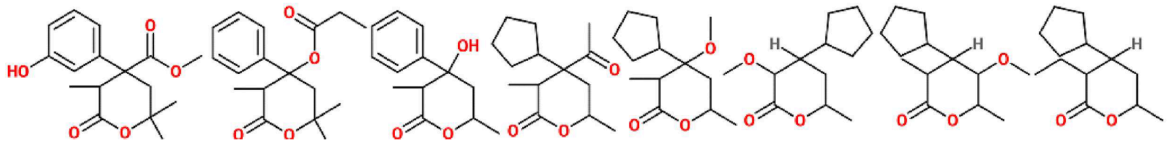
The drug design of such structures requires the use of special techniques to obtain correct pharmacodynamics, duration of action and other indicators. This work contains examples of the design of physiologically active alcohols, examples of special techniques, new nuclei, new pro-terpenes, new strategies for rational drug design:

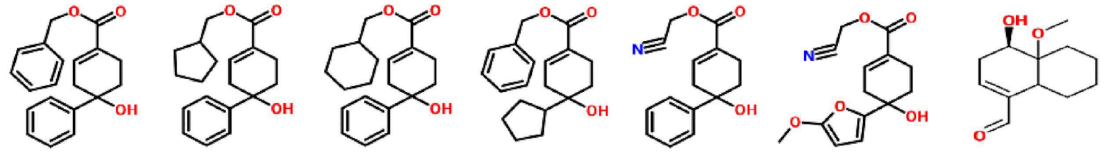




































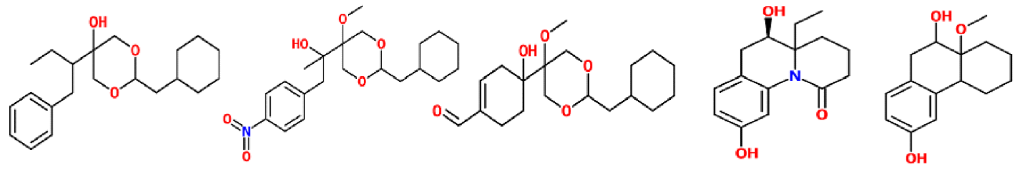


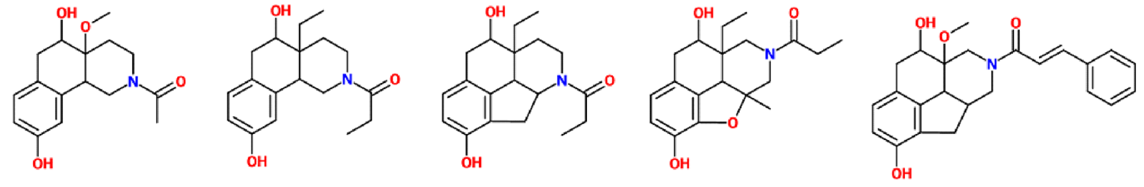


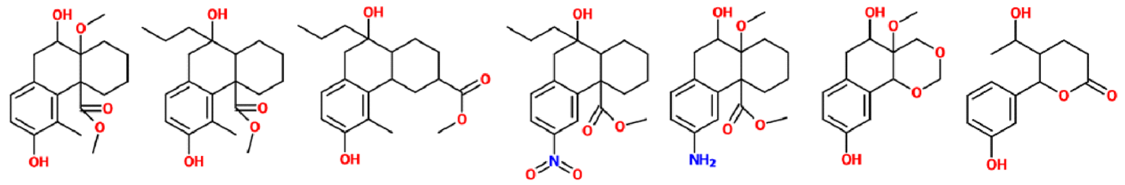


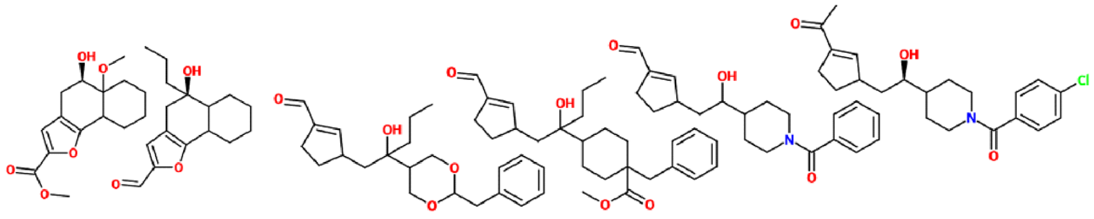


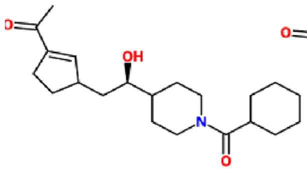
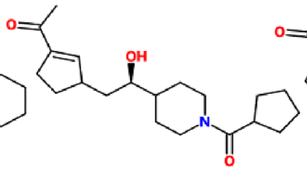
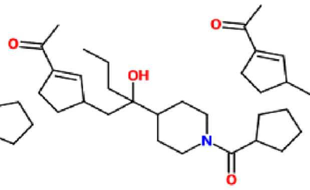
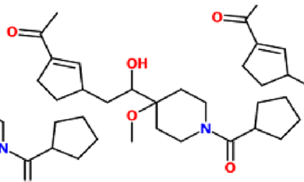
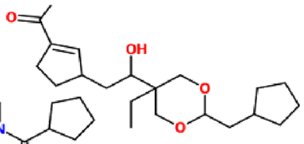
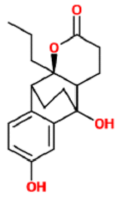
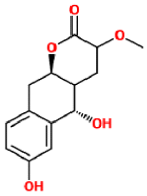
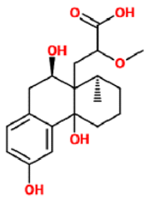
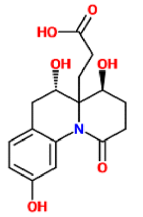
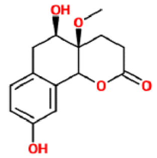
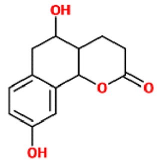
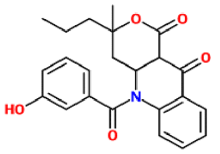
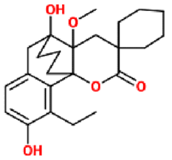
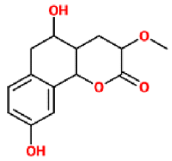
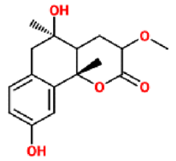
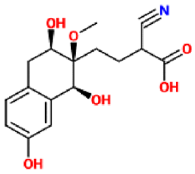
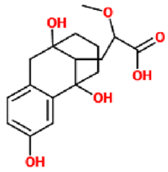
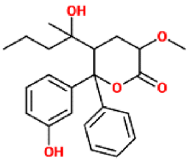
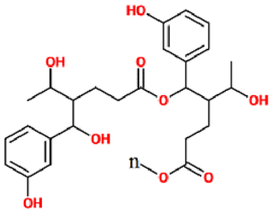
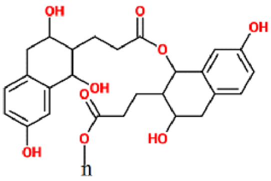
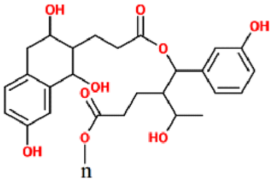
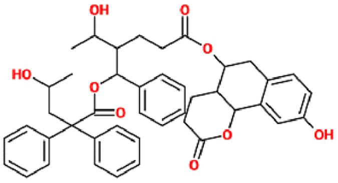
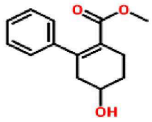
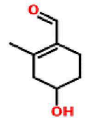
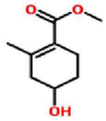
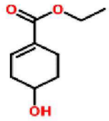
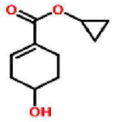
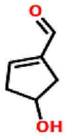
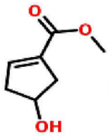
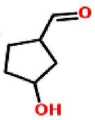
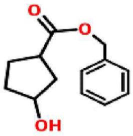
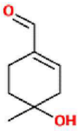
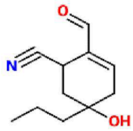
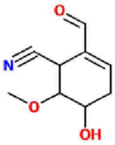
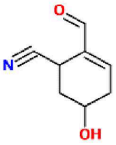
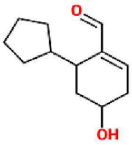
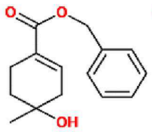
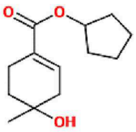
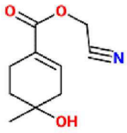
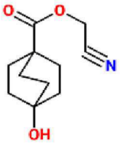
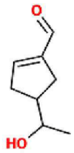
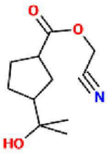
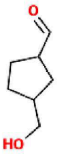
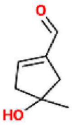
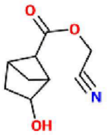
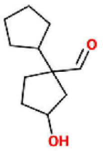
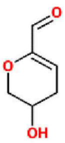
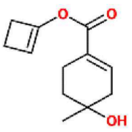
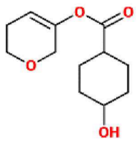
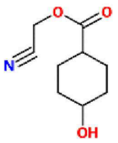
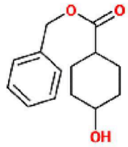
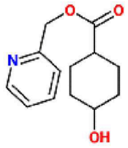
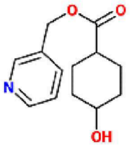
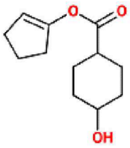
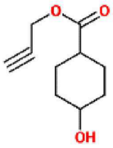
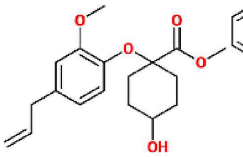
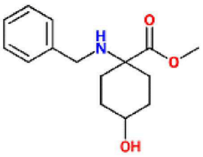
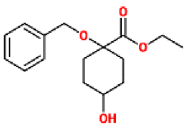
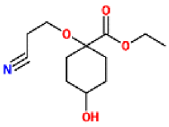
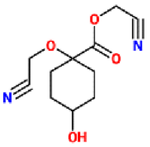
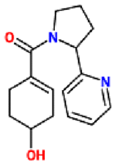
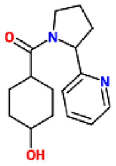
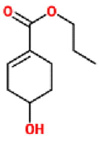
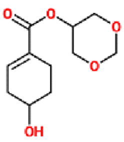
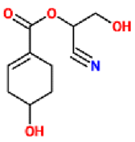


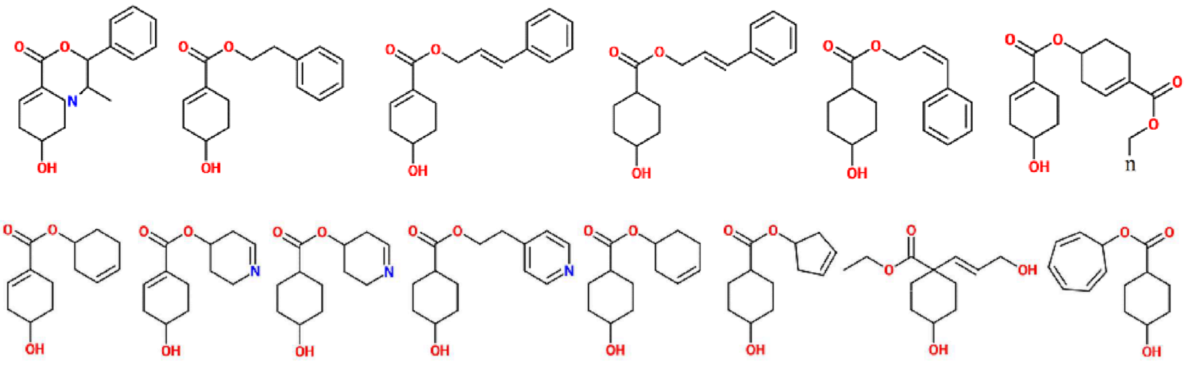










The diagram shows a rational drug design of analgesic alcohols, analgesic alcohols in combination with dopaminergic accents of picrocrocin derivatives, Crocus Sativus, and picrocrocin derivatives as potential dopamine reuptake inhibitors.

Among the substances presented in the diagram, there are examples of both high-affinity and extremely low-affinity substances. But almost all of the substances presented can have great potential as low-narcotic drugs, since the alcohol group, like the primary amino group, is less prone to potentiate powerful narcotic effects. This applies not only to opiates, but also to dopaminergics, although the latter do not act mimetically, but through dopamine, nevertheless picrocrocin demonstrates a very low narcotic potential, although it is a dose-dependent dopamine reuptake inhibitor.

So, ultra-light noticeable effects and the ceiling of maximum activity below lethal. Prospects for creating powerful but water-insoluble drugs unsuitable for injection. Pro-terpene nature of substances, from powerful terpenoids to ultra-light aromatic synthetic terpenes. Pharmacology of physiologically active alcohols can be extensive and contain a whole spectrum of previously inaccessible qualitative and quantitative indicators.

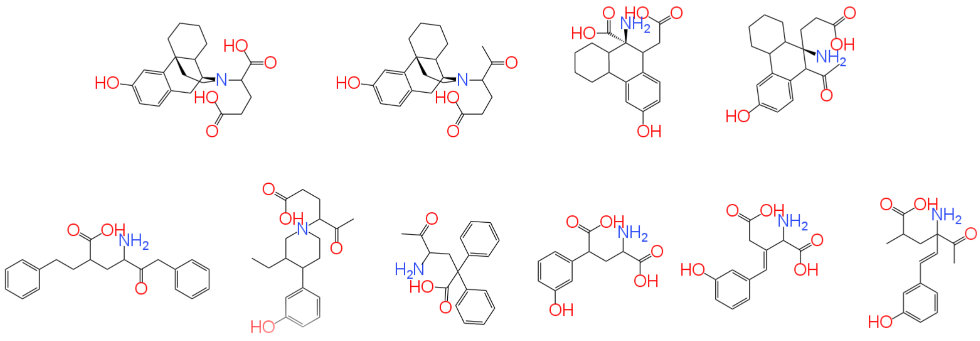
# Possible atypical kappa opioid, agonists of NMDA receptors.

The duplicate kappa opioid subsystem associated with a special response to the glutamine receptor is probably not fundamental in relation to whether the substance will be an agonist or antagonist of NMDA receptors. If you analyze kappa opioids, their structures are completely devoid of radicals close to glutamate, which can be the cause of the antagonistic effect. After all, when absorbed on the receptor, the environment of the amino group blocks that small part of the receptor that is responsible for recognizing glutamate.

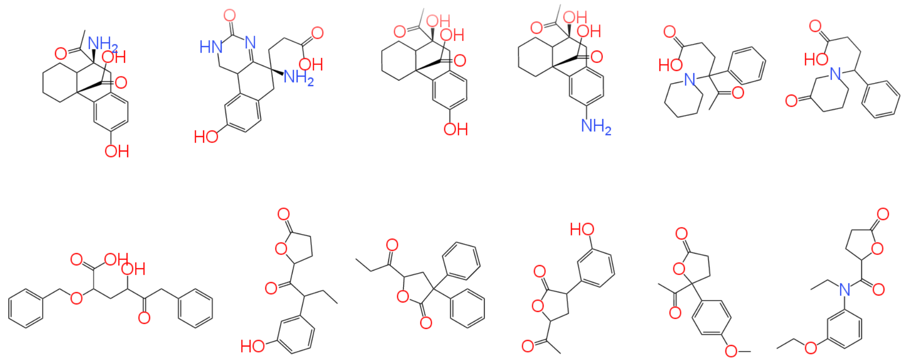
As a result, such selective kappa opioids as dextromethorphan or ketamine block the cluster responsible for recognizing glutamate, but adhere to it and to the cluster responsible for the duplicate kappa opioid group.

Accordingly, kappa opiates, in the structures of which radicals corresponding to the glutamate molecule would be located, could shed light on this issue and possibly provide a new class of drugs - kappa opioids, NMDA receptor agonists.

The design of such drugs is presented in the diagram, as derivatives of morphine, fentanyl, pethidine, promedol and methadone, which can be partially active and as mu opioids:



As a pro-glutaminergic fragment, not only derivatives containing an amino group can be used, but also pro-terpene glutaminergic fragments close to thujone or nepetalactone, or their pharmacological analogues:



This work was created as a first step to fill the gap in pharmacology associated with the rarity of pro-glutamate radicals in synthetic and natural substances, perhaps due to this factor, among kappa opiates only glutamate receptor antagonists are known.

Also, as kainic acid demonstrates, special selective reactions of glutamate receptors are possible. Because different types of glutamate receptors have different topologies and are composed of different functional subunits, a rational search for kappa agonists can rely on known kappa opioid cores and their variable reads.

At a rational depth of design, the prospect of setting up an experiment to discover agonistic variations of kappa opiates, as well as the discovery of a number of drugs with special properties, opens up. This work is a first step toward the stated scientific goals.

# Powdered tea from Hypéricum perforátum(St. John's) wort as a remedy for depression.

Powdered tea from St. John's wort as an effective, rational and cheap remedy for depression, with a good taste, in convenient packaging. The work was carried out at home, the results of the studies are easy to check using modern analytical chemistry methods.

Powdered tea was developed based on the physicochemical properties of the active substances of St. John's wort.

The main active substance of St. John's wort is hypericin (ill.), a red dye that has eight cycles, six phenolic groups and two ketone groups. This is a fairly water-soluble substance, if we are talking about low concentrations of hypericin. Hypericin as a dye manifests itself through color, this makes it easier to work with hypericin.

If you grind well-dried St. John's wort in a blender, then sift out the twigs, and grind again in a blender, you will get powdered tea. This tea gives all its color in boiled water. If you brew powdered tea a second time, you will see almost pure water. The common tea gives color if you brew it four more times. Thus, powdered tea is an active preparation. Powdered tea is several times more active, since fine grinding improves access to substances in the leaves, and resinous substances retain hypericin in leaf tissues.

It is also rich and tasty, if you add milk and sugar, it is similar to black tea with milk.

This is a good option for high-yielding varieties, this method allows you to avoid overloads, and use raw materials with almost no loss of the active substance. Simple, cheap, tasty and effective.

Powdered tea is easily filtered and can be packed in tea filter bags.

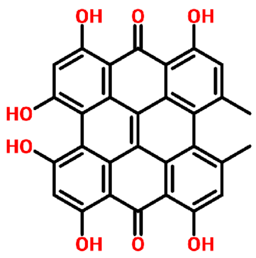
Powder as a method for increasing extractability and properties is not new, it came from China to Japan along with Zen Buddhism and founded the tea ceremony. In the case of the herb, the powder method of St. John's wort is much more effective because caffeine, unlike hypericin, is very soluble in water, and also there are much less resinous substances in tea.

Judging by the lack of color during the second steeping of the powdered tea in boiling water, it can be assumed that the powder method allows you to get the active drug, bypassing the extraction with organic solvents and pharmacological packaging. I also have a lot of experience with powdered tea, and I feel it is a very active and pleasant drink.

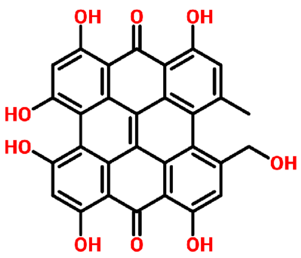
When using high-quality varieties of St. John's wort, 0.05% hypericin, the effective amount of powdered tea can be two grams. Which corresponds to the content of one milligram of hypericin, this is the daily dose of the drug. When using medium-effective varieties of St. John's wort, the daily dose is about several cups of tea.

Standardization of powdered tea is easy, as powdered tea has no losses during extraction and does not require additives for extraction, and is bioavailable, being a fresh solution of active substances. It is enough to measure the percentage of hypericin in the powder batch and the hypericin content in the cup and adjust the weight of the tea bag.

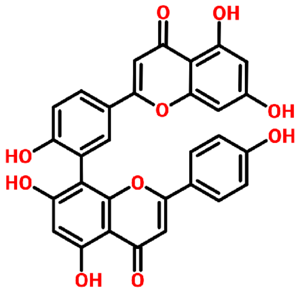
Illustration:



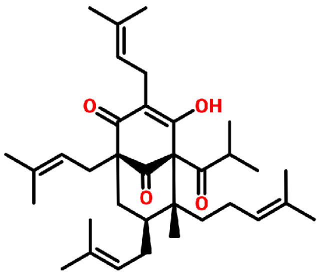
Hypericin



Pseudo hypericin



Amentoflavone



Hyperforin

Also, such a method may be somewhat selective in relation to the extraction of water-soluble substances, to a greater extent hypericin. Perhaps the powder method will be more effective as a selective dopaminergic antidepressant.

It is worth considering the negative aspects of using Hypéricum perforátum, such as increased sensitivity of the skin to ultraviolet light, possible gastrointestinal reactions with prolonged use, and also possibly minimal effect with repeated treatment.

But Hypéricum perforátum has a number of advantages even in relation to most pharmacological drugs. Hypericin is a dopaminergic, dopaminergic antidepressants are few in number, and such drugs often have a high market value.

Hypéricum perforátum is an inexpensive herbal raw material, but powdered tea based on it, according to the researcher's experience, has a relatively high-quality dopaminergic and antidepressant effect, which can be easily comparable with saffron or perhaps even with levodopa or other dopaminergics. Probably, Hypéricum perforátum can also be used for a short course in Parkinson's disease, possibly together with Saffron, since they strongly potentiate each other. But such subtleties require careful verification, as does the effect of multi-component mixtures on antidepressant activity in repeated courses of treatment for depression.

Also, such a method can clarify the pharmacological features of the main components, such as hypericin and hyperforin. And even more, for example, after brewing tea, it is possible to perform extraction again, after drying, extraction with vegetable oil and obtain two extracts, water containing hypericin and oil containing hyperforin. Such technology is also extremely simple and allows you to create an oil form that would contain virtually no hypericin, and this, in turn, could cancel some of the side effects, such as photosensitivity, thus removing most of the limitations of this useful and promising plant.

# Prospects for saffron as a means of increasing dopamine in marijuana users.

Both alcohol and marijuana are known to be partial depressants, and it is also known that marijuana can reduce the amount of dopamine, which can reduce motivation and activity.

It is logical that if necessary, it is possible to use dopaminergics to correct the condition of marijuana users, but is there a pharmacologically correct solution to this issue? Among the legal, over-the-counter and available dopaminergics, there are several natural remedies, carbidopa and saffron.

While carbidopa has been available for a relatively short time, saffron has been used for thousands of years, is the king of spices, and is a valuable traditional medicine. Saffron grows in many latitudes and can fully meet the increased demand. Saffron has proven dopaminergic activity and is a dose-dependent dopamine reuptake inhibitor, which puts it next to pharmacological dopaminergic antidepressants.

Saffron has a recreational potential and easily forms a culture of consumption, unlike cocaine, it is not a powerful drug, and unlike psilocybin mushrooms, saffron is relatively safe, extremely safe for the psyche.Saffron can be used in cooking, drinks or even smoking.

More details about the pharmacology of saffron are described in my other works.

Could saffron become a mainstream product in the world of cannabis legalization, microdosing and biohacking? Definitely yes, it can grow in every flower bed and it looks like it's time to plant Saffron.

Is it true that saffron is worth its weight in gold? In order to consume one saffron flower every day, it is enough to harvest from several square meters of land. From such an area you can collect some strawberries, for example, it is commensurate with a bucket of strawberries. The issue of price is conditional, saffron is very active pharmacologically, it is used in negligible quantities, so saffron can be considered a very generous plant, with a very large relative yield, which makes it very promising for cultivation.

Saffron blooms beautifully, its flowers are a pleasure to collect, and there are more saffron bulbs every year. As a result, in places of growth, saffron bulbs become excess material for planting, and saffron itself becomes a free spice that does not require special care.

It also makes saffron related to marijuana.

# Rational drug design on the example of light cannabinoids.

The drug design has several branches of development, such as irrational selection, rational search and newer layering, computer subtraction, mapping of biological objects, simulation of the target and the drug.

One way or another, the share of rational search and human intellectual activity in the process of developing the design of preparations is, as before, great. And also in some cases modern methods of computer modeling can be greatly overestimated, for example, when developing high-affinity mimetics, there are known cases when extremely affinity mimetics were developed in the pre-computer era, probably this may also apply to light drugs.

Biomolecular mapping and mathematical models are not able to replace the accumulated experience in the design, and as a result, the drug design develops new theoretical methods. One of these methods is to regulate the activity and strength of the drug, through the use of radicals with more or less complementary interaction forces.

The degree of conformity of the chemical compound drug and the target is measured by several quantities:

This is the geometric correspondence of the placement of the necessary chemical radicals. This is a quantitative match and a qualitative match. As well as compliance with the degree of mobility, the dynamic behavior of the molecule. Regulation of the activity of a substance is an important parameter that allows you to create drugs with convenient dosage or high safety.

To achieve high safety performance, a method of reducing the energy of the bond between the drug and the target is used. This approach makes it possible to establish a low ceiling of maximum activity. Even in case of overdose. These drugs show low activity, which eliminates the development of critical side effects.

This method, one way or another, is used in the development of most drugs, but is particularly relevant in the development of centrally active drugs. The molecular mechanism of this approach simulates small concentrations of natural endogenous substances and this happens as follows:

A molecule with reduced binding energy by binding to the target gives a signal corresponding to the endogenous hormone, but this signal is weaker. Because such a chemical molecule is not able to be strongly fixed on the target, in the dynamics this process looks as if the target attacked the native hormone in a small concentration. Innervation of the synapse occurs, but it is reduced, even with high concentrations of the drug, because it is not able to give a strong signal in principle. Drug radicals do not have a large "stickiness", they cannot group around themselves the tissue of the receptor, the receptor at a certain moment unloads kinematically, envelops the drug, but quickly returns to its original, not active, position. This process is not related to the concentration of the drug, it is related to the design of the drug.

Also, the size of the drug(molecular weight) can have a similar role, if the activity of a substance is considered as a dynamic process: A drug with a core that is much smaller than a native mediator, a hormone.., can imitate a mediator... Moving in the active zone of the target and alternately attracting complementary points, performing a complex movement, it contributes to the kinematic receptor unloading, the target gives a signal and relaxes, some time passes and everything repeats again.

Or the signal is generated permanently, but has a low level due to the fact that the substance is not able to consolidate all the complementary points of the target in a consolidated manner. In any case, we get the nature of the signal close to the low concentration of the native agent.

Separately, it is worth noting the necessary balance of complementary points, a strongly complementary radical can provoke a high activity of the drug. When developing weak drugs, with a low ceiling of activity, the radicals should have a weak "stickiness", the core should not be massive and "sticky". Complementarity should be evenly reduced, or it should be reduced in the critical area. As a rule, this is the area that determines the key signal or the signal of the agonist/antagonist.

The features of these specific points are determined by the nature of the receptor and substrate, the precursors of substances from which the native active substance is synthesized and the decomposition products of this substance. These are logical guidelines for virtually any type of target. The substrate recognition scheme is associated with substances of a similar nature that are in the body. Thus, nature makes the target selective and does not allow a false signal from specific intermediate metabolites inside the body.

And it can be a source of information or assumptions about that, what can be an antagonist and what should be an agonist. For example, fatty acid metabolites are not recognized as endogenous cannabinoids, meaning that carbonyl group-duplicating radicals can block the activity of the endocannabinoid mimetic.

There is a higher selectivity, it is dictated by the fact that for some endogenous hormones there are many receptors in different parts and organs of the body. In the process of evolution, these receptors have changed, but they continue to absorb the same hormone. This makes it possible to influence only our chosen receptor.

Such targets have a number of spatial differences and assume selectivity dictated by these spatial differences.

Substances that have certain spatial interference can be sorbed by one type of receptor, but cannot be sorbed by another type of receptor. That is why cardiac selective drugs have a molecular mass much more than adrenaline. Adrenaline is not a selective agonist for these targets. A small antagonist would be a nonselective antagonist. But a molecule with a large mass and spatial noise at the right points becomes a selective antagonist or selective antagonist, since the active zone of the receptor has a different landscape.

Places for adrenaline on the target surface are greater than the magnitude of the adrenaline itself. Although this space is rocky, it also suggests additional places for sorption. And this makes it possible for such maneuvers, and even possible to enhance the complementary attraction, because the more areas for "sticking" the stronger the signal. And it is possible that in this way it is possible to develop drugs that will be even more active than even natural neurotransmitters or hormones (if necessary).

For example, in the case of anti-cancer cannabinoids, the shock activity of cannabinoids in relation to the target may be useful. And in the case of non-narcotic cannabinoids, this therapy can be quite painless.

Thus, even without accurate mapping, using a non-rational and rational design drug, many preparations with specified parameters were obtained. And can be obtained in the future using more detailed techniques. And all the strategies of rational drug design were developed by human intelligence, which remains relevant today, at the very top level of strategic decision-making in the field of drug development.

This work is devoted to light cannabinoids as a likely promising and new matter for drug design. Some mistakes have been made in the development of synthetic cannabinoids: this is a large molecular weight and does not correspond to the geometric parameters, in favor of simple chemical synthesis. Some well-known chemical molecules of synthetic cannabinoids have the inclusion of pro-opioid radicals (piperidine). Often, synthetic cannabinoids are poorly balanced, have less than ideal pharmacokinetics, and at the same time, high affinity. This is the reason why the black market of modern synthetic cannabinoids is so dangerous. This creates problems when using cannabinoids in pharmacology, pediatrics.. This complicates the use of cannabinoids, because it repels the state apparatus from the use of marijuana or cannabinoids.

The market for cannabinoids, marijuana, is growing and, accordingly, there is a growing need for understanding the mechanisms for developing highly safe drugs.

Opinions of the average man divided, from approval to rejection. From the opinion that medical marijuana is harmless and the best medicine from the list of cannabinoids and other drugs, because it is a natural medicine... And to alertness, because cannabinoids have side effects and are difficult to integrate into pharmacological practice.

Society does not have objective data and does not have the best examples for analysis. Let's broaden our horizons a bit before considering a drug design cannabinoids:

I want to destroy two myths. The first myth: Marijuana is a plant material and it is the safest. The second myth: there are no light synthetic drugs, all chemistry is heavy and dangerous.

1. Chloroacetic acid is also a natural product, although it looks more like chemical weapons. Botulotoxin is a natural product but it is the most toxic agent.

On our Planet Earth lives one percent of the entire diversity of species that was before. Some plants have survived until now, such as ginkgo biloba. This plant gave amber, but also high-quality nootropic. There were many such plants, perhaps some synthetic drugs are natural, but we do not guess it.

We also know that there are probably millions of planets in the world on which there are oceans. And what plants are likely to grow on these planets. It looks like a reality, and probably natural substances are millions of times more than we think now.

2. Among plant cannabinoids there are lighter than THC, it is beta-caryophyllene, but it is not very suitable for use. Synthetic cannabinoids have a non-quality drug design. This is done in favor of chemical synthesis. Also dangerous is the initially low level of drug design, multiplied by the lack of pharmacological education among the authors of designer homologues of synthetic cannabinoids, and the lack of long-term preclinical and clinical studies.

But synthetic cannabinoids can be of high quality and very light, not powerful, even with increased dosage:

Imagine the THC receptor, this is a kind of landscape, ready to take Anandamide. It does not work as a lock and key, it is more difficult. If you have a substance that simulates Anandamide, but in a weaker manifestation, with weaker radicals, a weaker pull energy, a weak complementary force of attraction. And even if they are much smaller than the original, anyway, they will open this door, but the momentum will be weak, even if you take a lot of this substance. And this approach mimics the low level of Anandamide. Even if you take a lot of this substance, it will not be able to give a strong signal level. Such substances are characterized by a low ceiling of activity and weak manifestations of action. This is a biomolecular mechanism that allows us to give mankind safer drugs, even safer than marijuana.

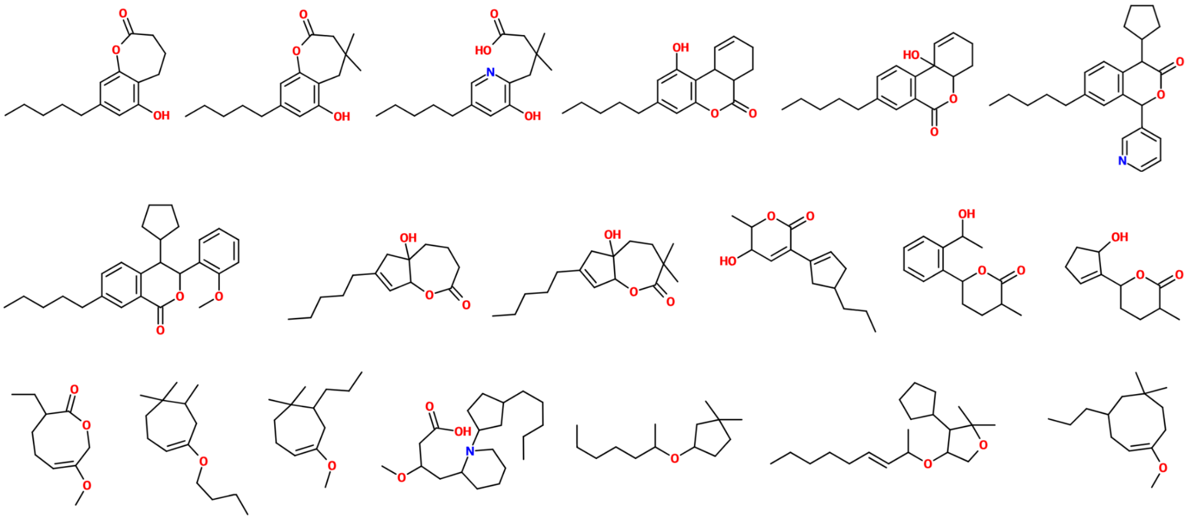
Well, now we see that the boundary between synthetic matter and natural is practically erased, and the issue of reliability is reduced to the quality of the design of synthetic matter, or how much nature has endowed us, and how much those plants that we have correspond to our goals.

And if your goal is to develop an easy and safe cannabinoid for pharmacology, pediatrics, psychiatry, and even for recreational purposes and legalization. In this case, we need to work not only on varieties of relatively safe medical marijuana, but also to radically change the qualitative properties of the drugs. Centrally active drugs, opioids, cannabinoids, stimulants, dopaminergics, this is the most difficult matter for the development of drugs, because the quality requirements of centrally active drugs are much higher and there much more.

Therefore, many methods and strategies are likely to be used for the development of light cannabinoids. The methods mentioned above, specific strategies for the use of radicals and nuclei, the principles of behavior are shown in the illustration.

In the illustration you can see both the radicals with low "stickiness" and the light nuclei, and a small mass of molecules, as well as the use of lactones and internal salts. All these steps contribute to a not high ceiling of activity and weak activity, even in large doses. And it is possible that a record of a high lethal dose of THC will be broken. And it will be impossible to obtain high-power, hallucinogenic doses.

Design examples:



As can be seen in the figure, the amide group (anandamide) is replaced by a ketone or dimethyl, which reduces the "stickiness" and increases biostability. Also, at the same time, small core, not pronounced simulation of ethanolamide. Since such substances include pharmacokinetics, bioavailability, half-life, catabolism, the design also includes elements of biostability and catabolism, water-soluble metabolites, inactive metabolites.. As much as possible, more detailed similar qualities are checked during the development of the drug, preclinical studies and clinical research. Clinical and post-clinical studies eliminate non qualitative effects and provide fine-tuned, specialized drugs for specific uses.

# Simulating effects of alcohol, using μ and κ opioid active alcohols.

Ethanol indirectly affects the GABA system, glutamine, dopamine and opioid system. Opioid effects of alcohol are significant. Is it possible to simulate the effects of alcohol by combining in two types of opioids?

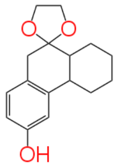
Definitely Yes, many natural and synthetic opiates have a dual nature but prevails impact on μ receptors or on k. Can complex opioid alcohols have such a structure to give a balanced result? Balanced opioid must be shifted toward dissociative activity. However, this substance should not be a strong anesthetic and analgesic. If pharmacology this material will allow us to obtain acceptable results, we will be able to get the drug that not only does not cause liver cirrhosis, but possibly not fatal in large doses, since there is a possibility of creating a light agonist with a low ceiling of maximum activity.

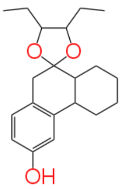
Some primary amines such as Dezocine, are positioned as very safe analgesics, and our alcohols are close to primary amines and are not as powerful drugs like strong analgesics.

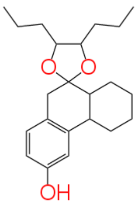
With regard to the possible opioid dependence of these drugs, it is worth noting that, without significant qualitative properties, an alcohol simulator is capable of being not competitive. But there is some wiggle room for a low-addiction drug, such as alpha terpineol, which is probably a pro-opioid, probably an ultra-light enkephalins mimetic, and it does not cause addiction or tolerance, and has not been implicated in fatalities.

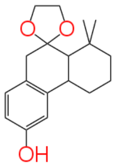
The drug should not be highly active, it should be safe and balanced. Then we will be able assess the prospect or define the absence of prospects for that matter. Alcohols as primary amine are little studied and they are difficult to design drugs, but they are ideal for producing lightweight mimetics and are worth demonstrating greater skill in rational drug design. Also, as a mimetic of the amino group of new classes of opioids, it is possible to use dioxolanes and esters, sometimes as minor effect modifiers, and also, in some cases, as the main substance.

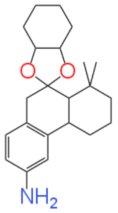
Examples structures:

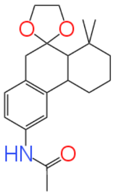


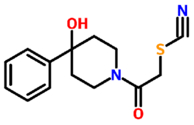


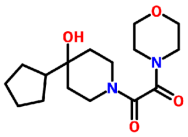


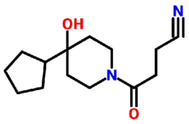


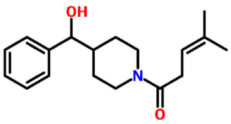


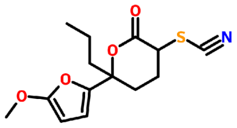
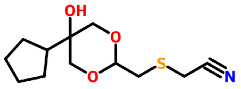
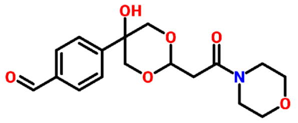
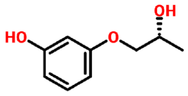
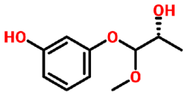
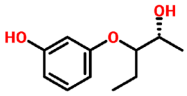
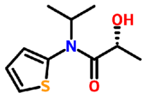
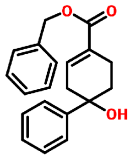
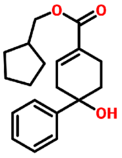
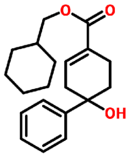
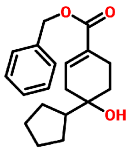
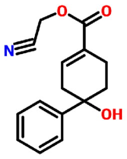
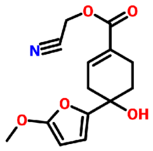
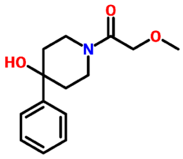
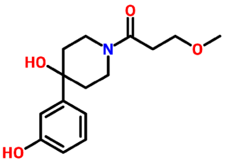
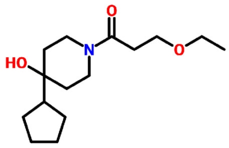
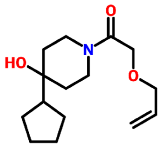
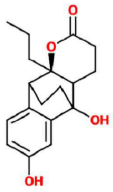
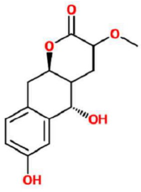
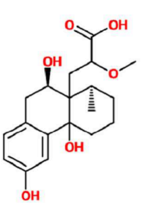
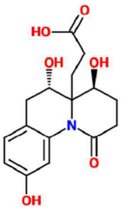
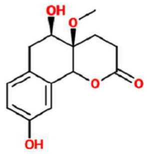
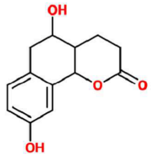
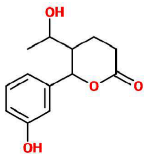
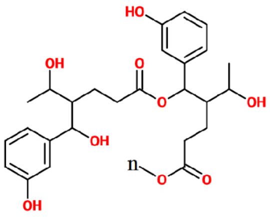
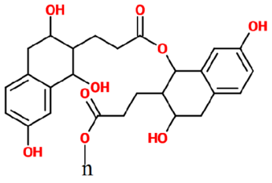
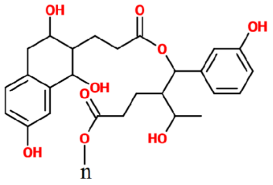
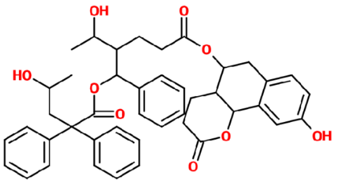










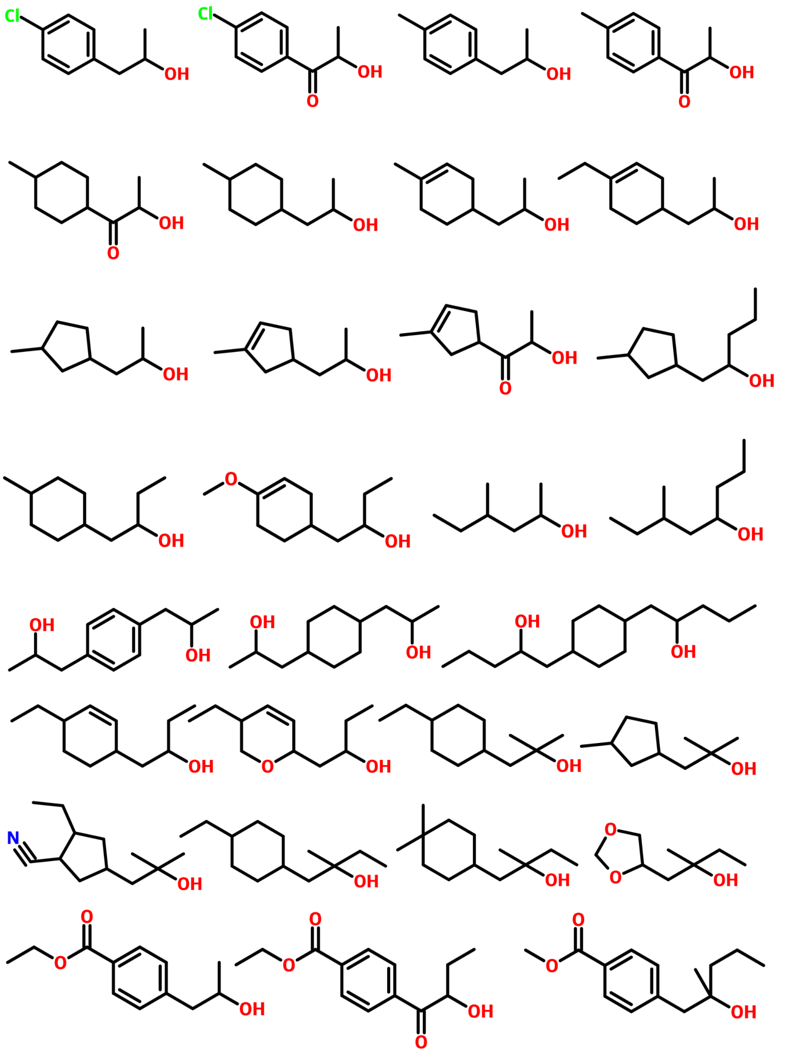





























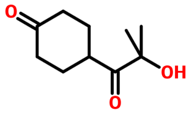
# Structurally similar to stimulants and antidepressants, alcohols as substances with possible anti ADHD potential.

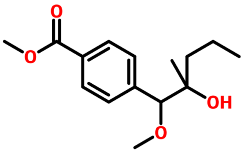
Physiologically active alcohols often have high activity and at the same time more gentle action compared with the same amines and alkaloids. Alcohols have some limitations when drug design, some structural features and their inherent potential side effects, but also have a number of positive qualities, which makes them potential candidates for the role of pharmaceutical drugs, with more careful consideration.

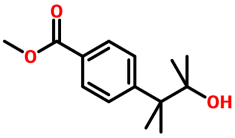
In this work we used simple examples of analogues of substances from the amphetamine group, to demonstrate pharmacological techniques which can be used in working with this matter.

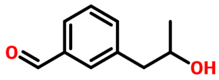
Examples of derivatives:

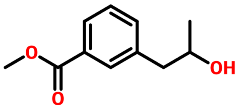


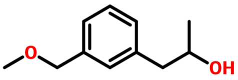


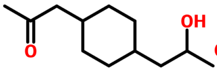


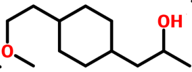


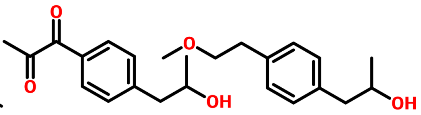


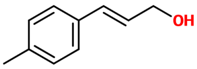


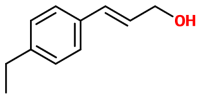


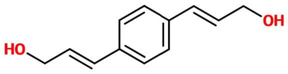


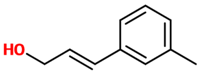


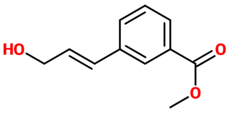


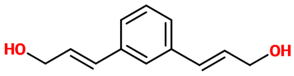












# Structures close to reuptake inhibitors neurotransmitters and serotonin.

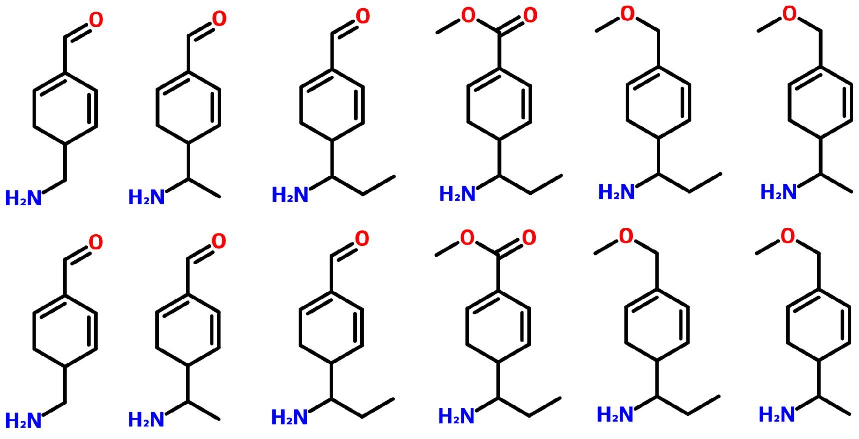
The aim of this work is to attempt to reproduce the likely design of inhibitors serotonin reuptake, using the design principle of natural inhibitors of dopamine reuptake, like cocaine, dehydroxy ecgonine(methyl ecgonidine, AEME) and picrocrocin(saffron, active ingredient of Crócus Sátivus).

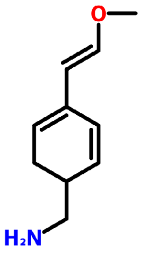
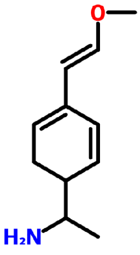
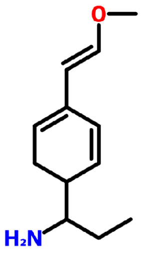
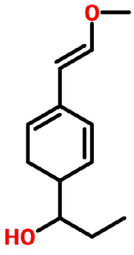
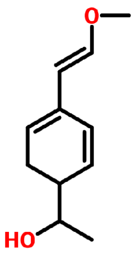
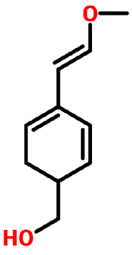
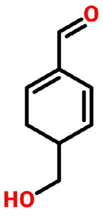
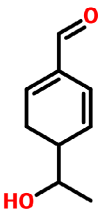
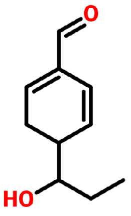
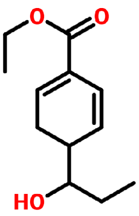
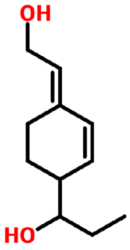
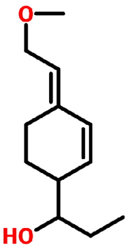
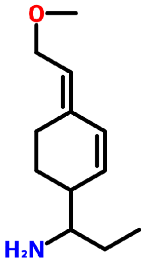
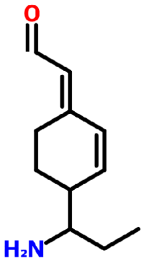
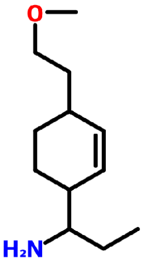
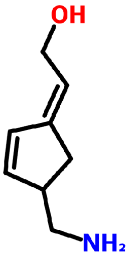
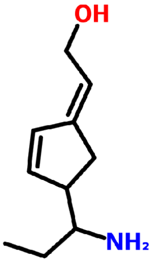
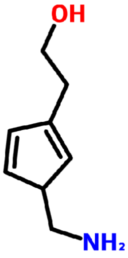
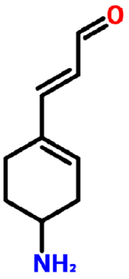
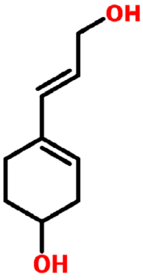
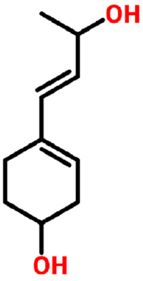
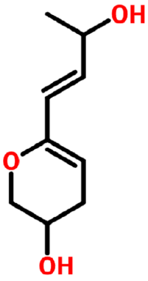
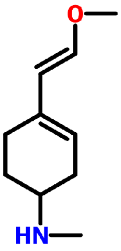
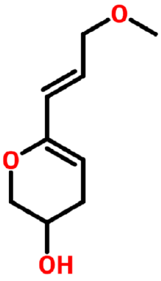
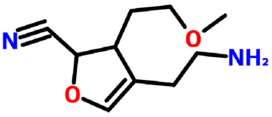
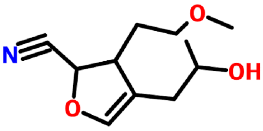
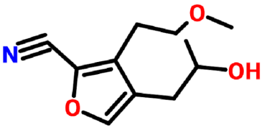
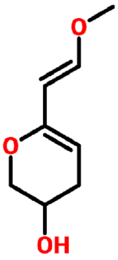
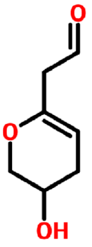
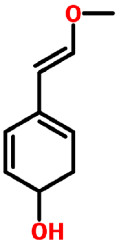
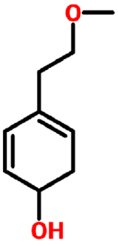
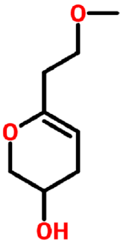
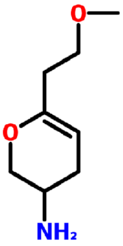
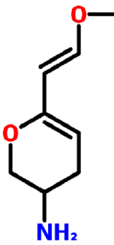
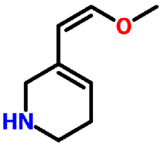
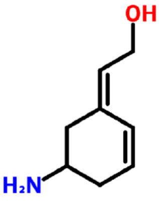
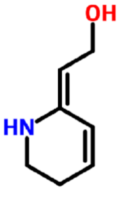
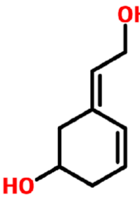
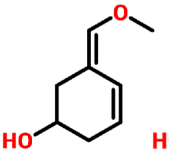
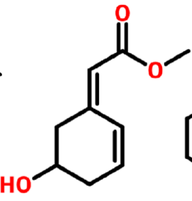
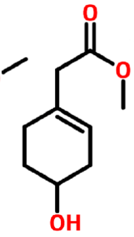
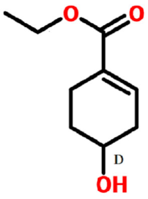
Drugs that increase levels of serotonin are popular in the pharmaceutical market. But among natural substances there are few good examples of serotonergic substances. Comparing the dopamine and serotonin reuptake protein (since we create substances with affinity to this protein) is not correct, because these proteins have completely different structures. But it is also true that such proteins have slightly different requirements for obtaining substances with affinity to them. As a rule, such proteins allow much more freedom for the structure of the neurotransmitter reuptake inhibitor, mimetics, as a rule, are much closer to the structure of the neurotransmitter than reuptake inhibitors. Thus, although the proteins responsible for the capture of neurotransmitters are completely different in their structure, due to the simplicity of this structure, they allow for a commensurately equal and relatively greater freedom and diversity of potential inhibitors.

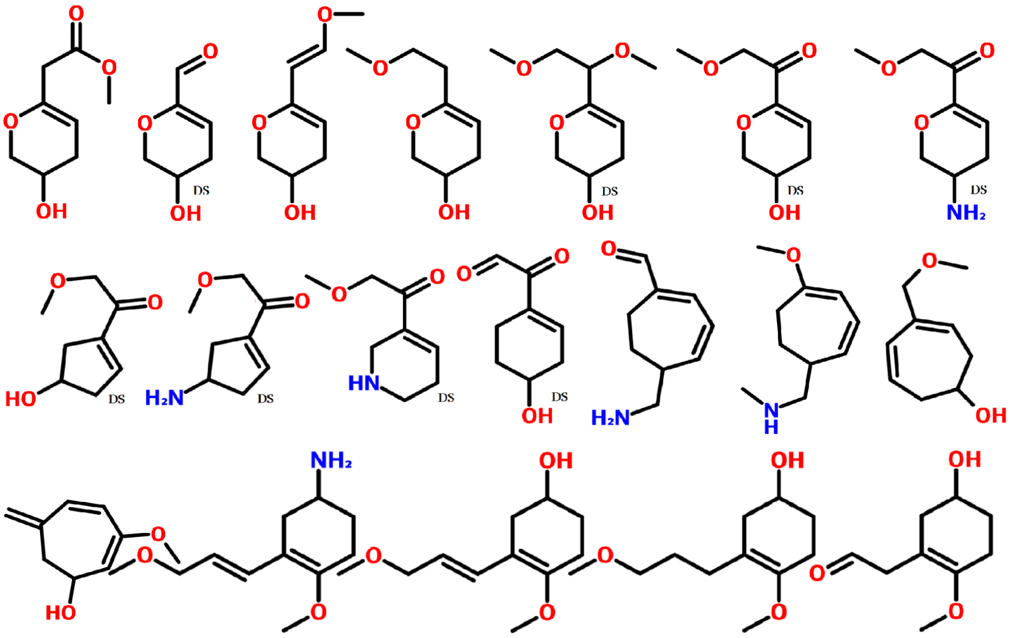
As shown in the diagram, the structures are extremely compact, often relatively biostable and bioavailable, are lipophilic enough, have some pathways for catabolism and can have satisfactory pharmacokinetics. Since the structures have only distant analogies of indole, created by the principle of transfer from the picrocrocin group, there is a possibility of high activity and conditionally high biostability of substances, without the involvement of halogen aromatic radicals. In fact, such works can open new active nuclei, with completely new properties, thanks to a rational deep approach to drug design. This work was created to test a new, rational and deeper pharmacological strategy, this work is a touchstone. Despite the fact that the number of serotonergic antidepressants on the pharmacological market is quite large, which means that the prospects, even in the studied areas, are not impossible.

Among the following serotonergic structures are present, and several such, they are marked with the acronym DS - dopamine, serotonin.

Examples of structures:



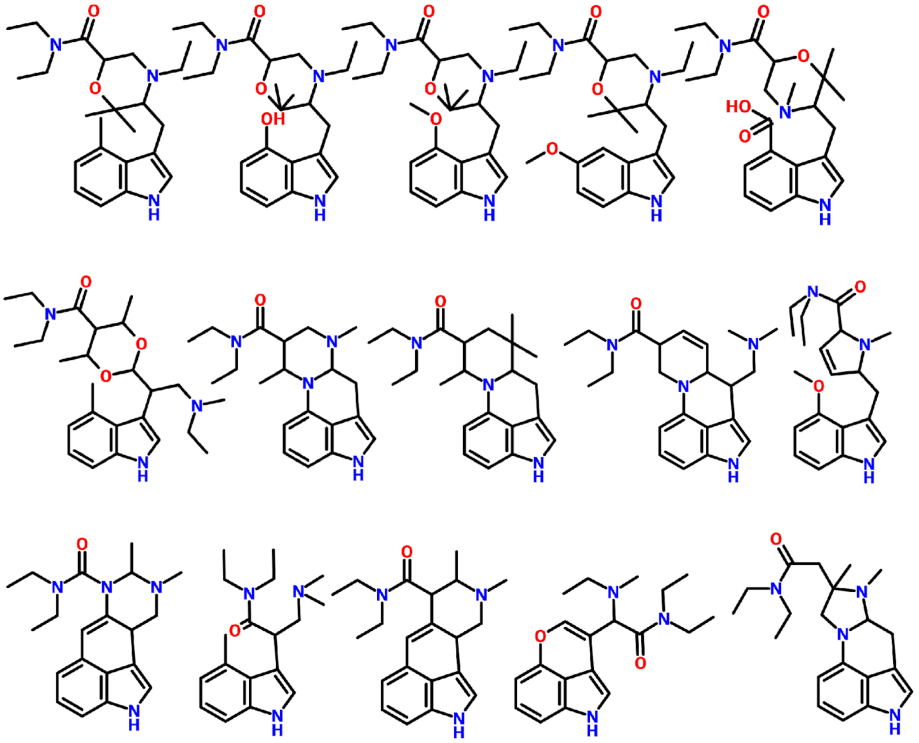


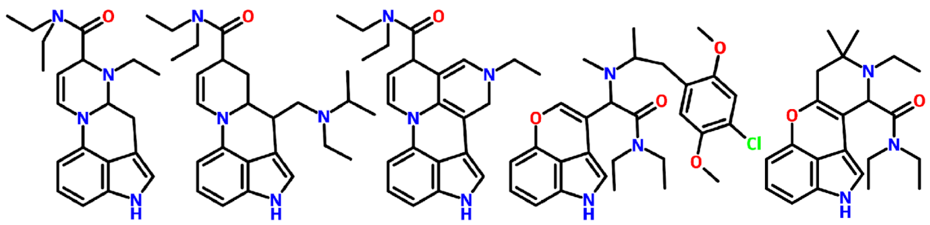
# Substances structurally similar to LSD, tryptamines and phenethylamines.

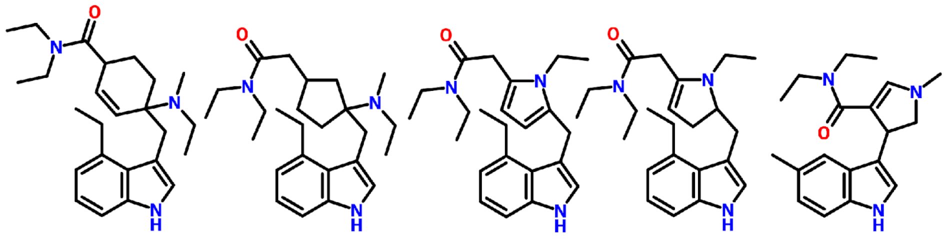
The aim of this work is the search of possible pharmacological analogues of LSD, tryptamines and phenethylamines, the search for new kernels, more convenient methods for the synthesis of more stable substances, substances with new properties.

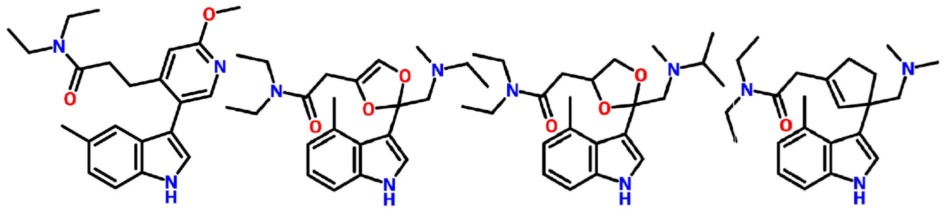
Since DMT, Mescaline and LSD have cross-tolerance but different pharmacokinetics, for example substituted phenethylamines have a half-hour lag before the development of psychedelic effects. It is possible to conclude that Mescaline has a cumulative effect in relation to endogenous psychedelic neurotransmitters, LSD and Tryptamines accordingly can be active as mimetics.

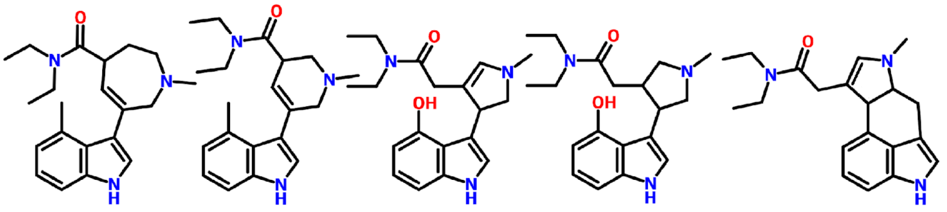
Such an idea asks the question, where are the DMT and Bufotenine reuptake inhibitors? An attempt to answer this question is completed by the series of structures below, with possible reuptake inhibitors listed at the end of the list. Below are derivatives close and relative to LSD, with new degrees of freedom and drug design strategies. Also presented are examples of substances similar to Mescaline, some of its synthetic analogues and substituted tryptamines. All these substances are not simple derivatives of known substances, each example is a new reading, a new core, the structures smoothly flow into one another, drawing out more and more new strategies for the implementation of the psychedelic substance, which is not surprising, because we are talking about mimetics and inhibitors of the reuptake of two extremely similar endogenous neurotransmitters - DMT and Bufotenin:

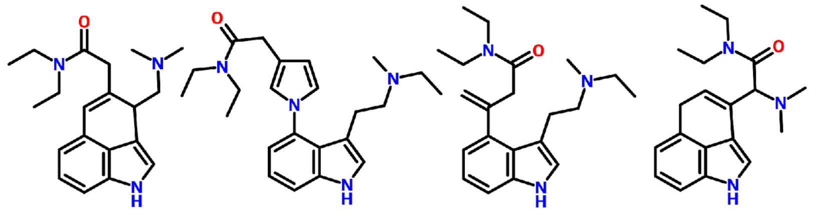


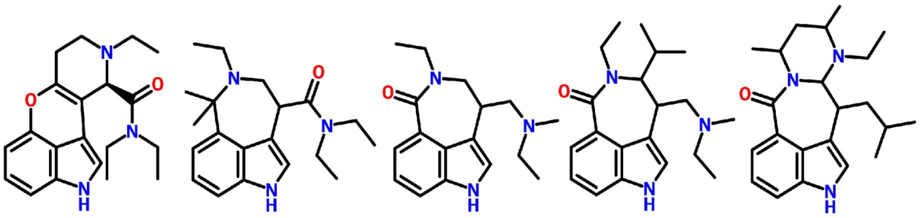


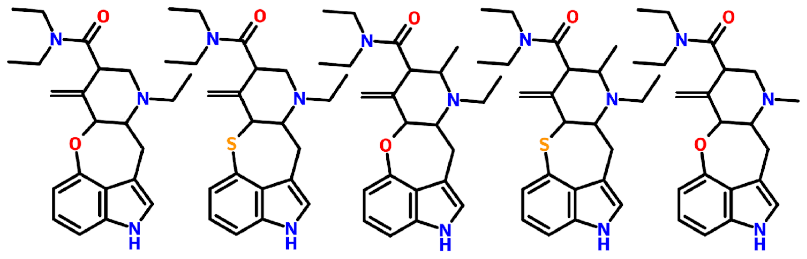


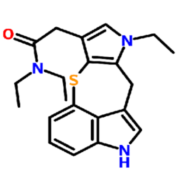
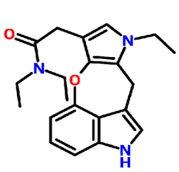
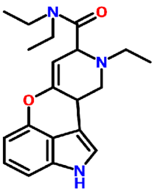
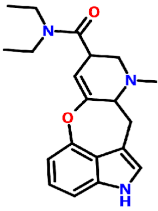
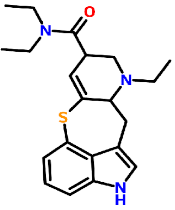
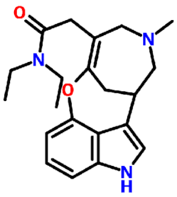
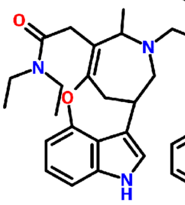
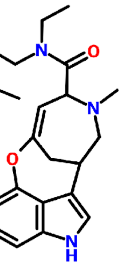
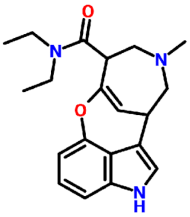
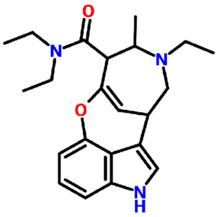
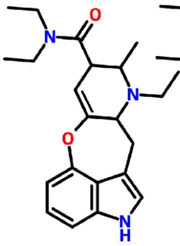
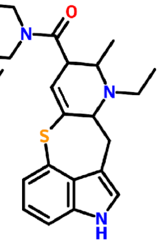
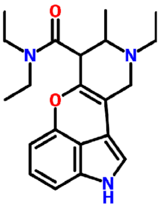
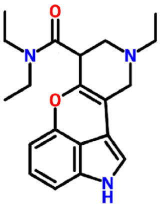
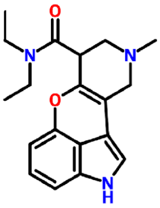
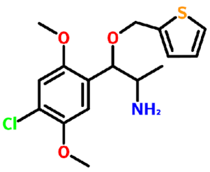
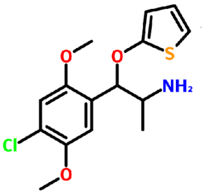
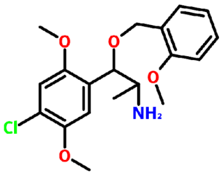
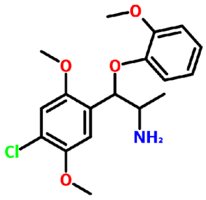
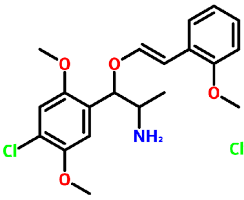
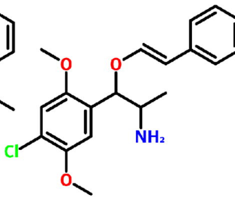
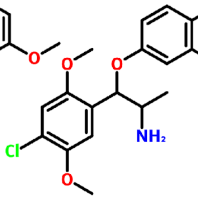
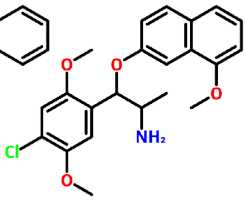
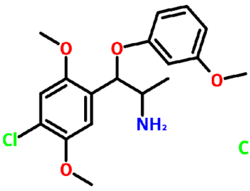
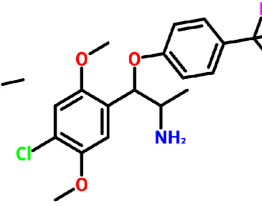
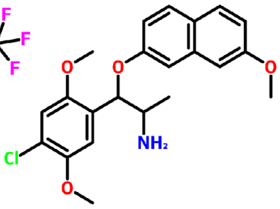
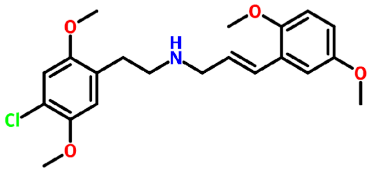
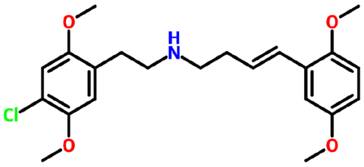


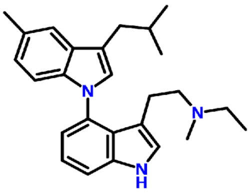
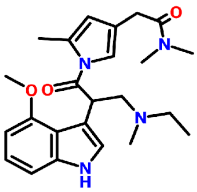
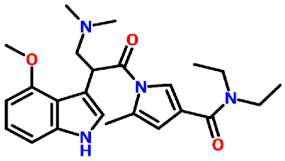
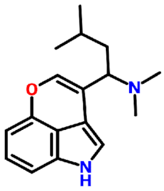
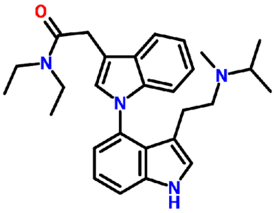
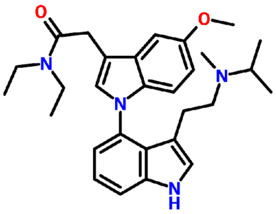
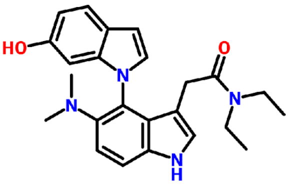
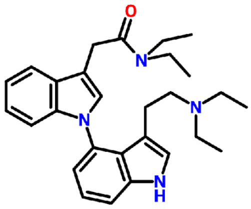
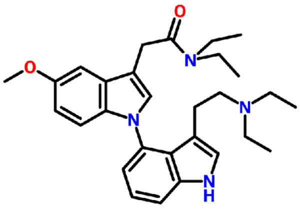
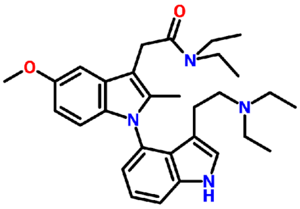
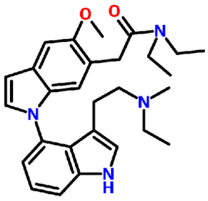
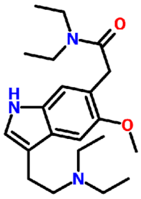
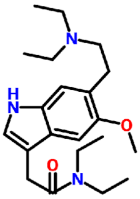
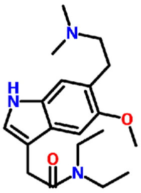
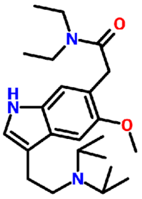
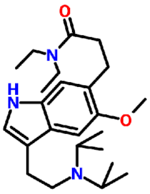
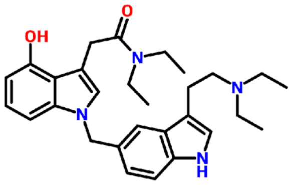
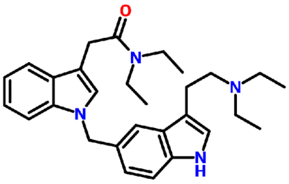
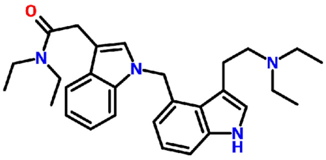
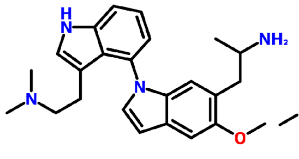
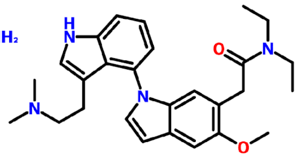
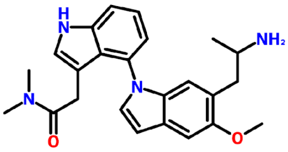
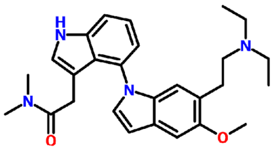
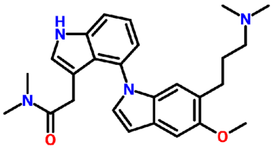
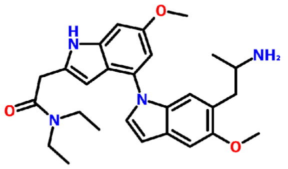
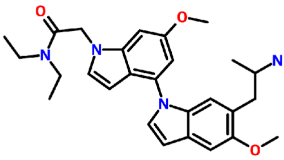
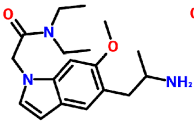
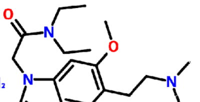
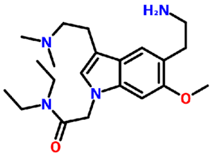


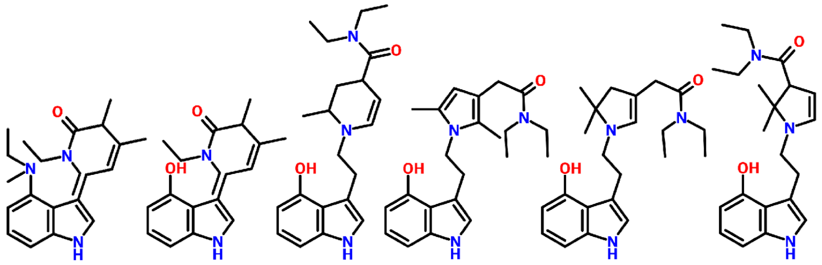


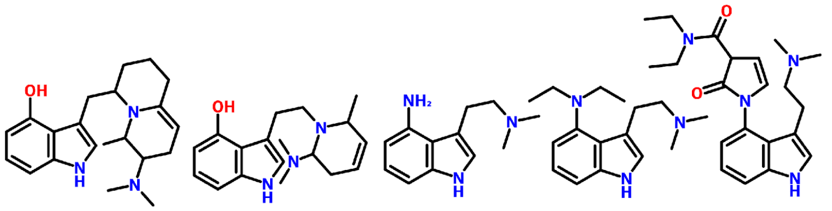


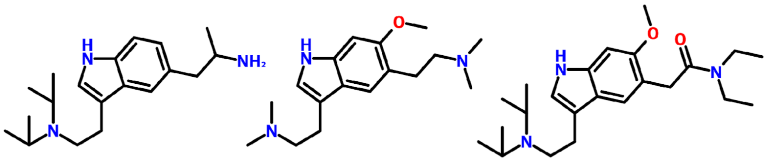


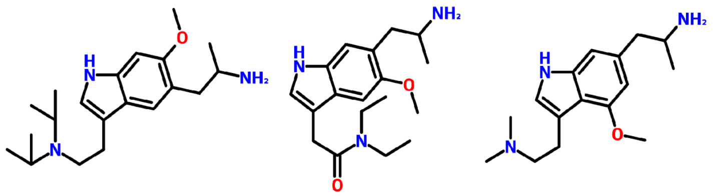





























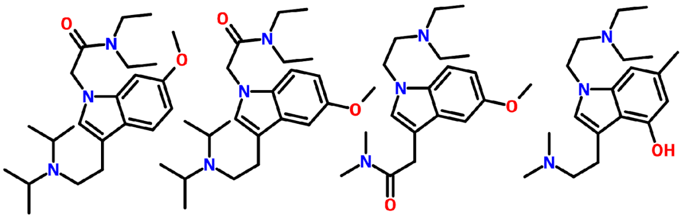






























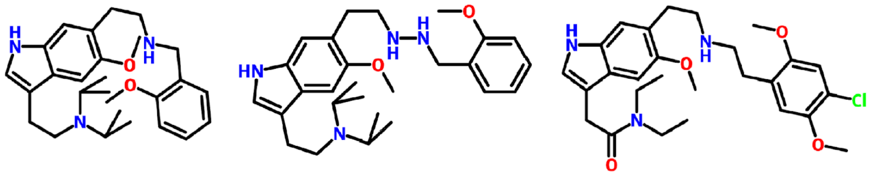


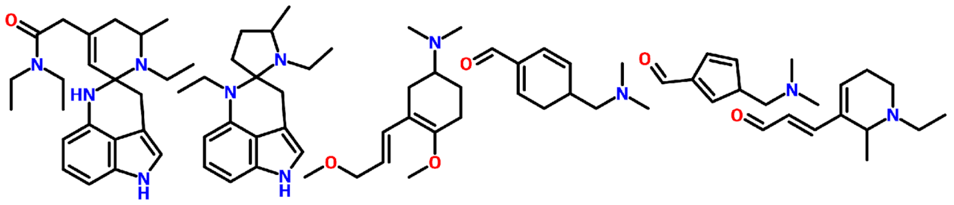


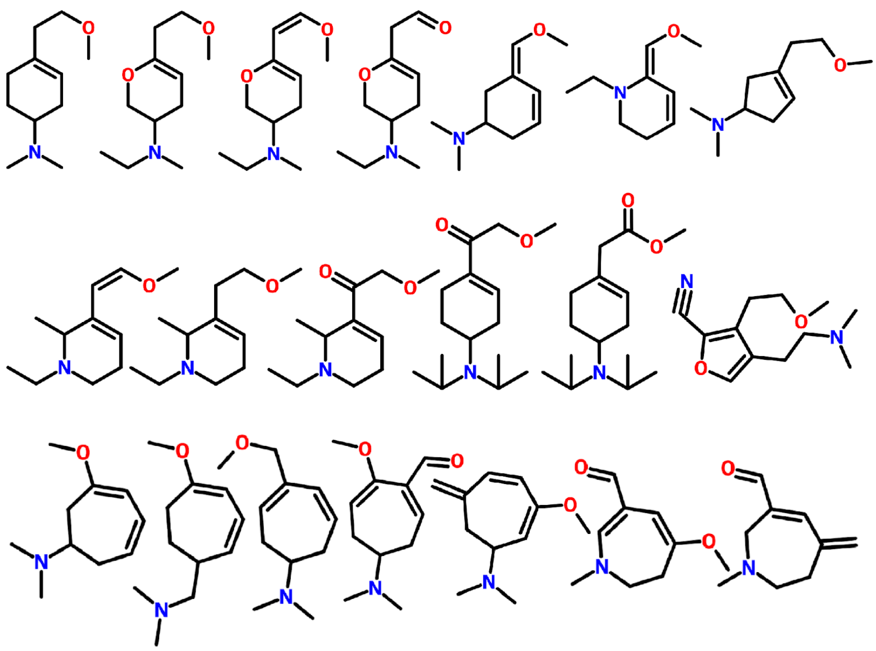










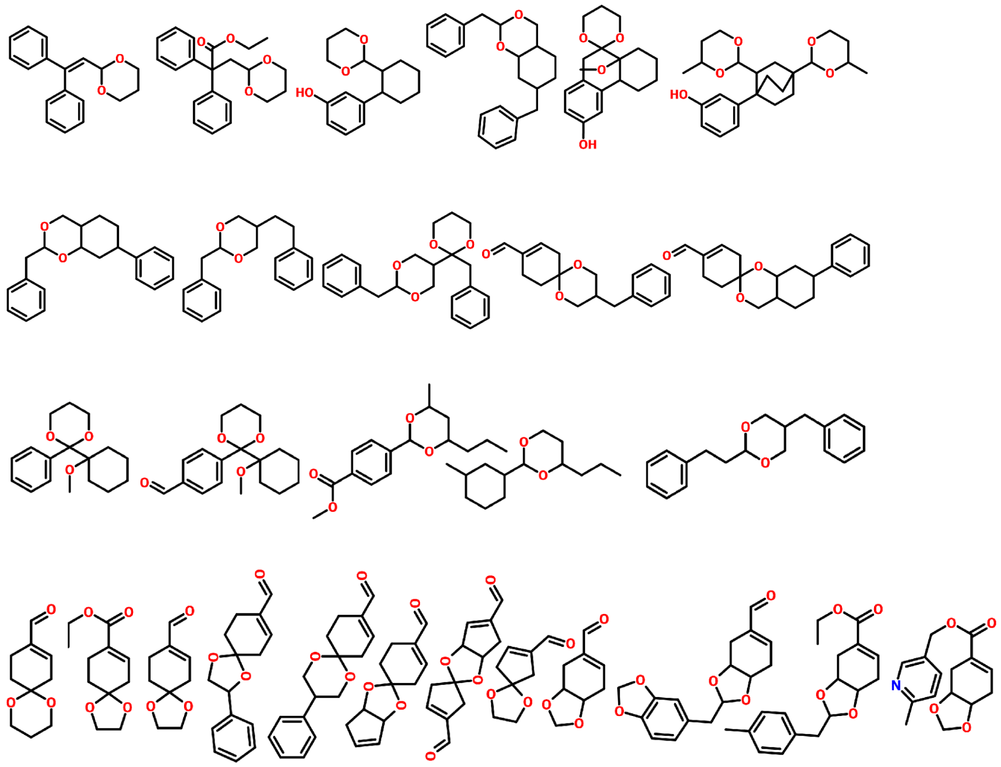


# Substituted 1,3-dioxolanes, structures close to analgesics, anesthetics and dopaminergics.

Dioxolanes can be physiologically active. Of interest are such physiologically active substances, that are not among natural and pharmacological substances. Dioxolanes are extremely rare among physiologically active substances, although dioxolane derivatives have the potential for direct mimetic activity.

1,3-dioxolanes are convenient for the synthesis and planning of catabolites. The results of studies of these substances can present both surprises and original parameters and properties, for example, especially light mimetic properties, reduced affinity and narcogenicity, tolerance and addiction, as well as a low ceiling of maximum activity and a high delta between the active and lethal dose. All this can contribute to the safety of opiates, which is difficult to implement, but possible within certain limits. New nuclei, new drug design strategies, new examples can expand the limits of possibilities.

The figure shows the structures of analgesic, anesthetic and dopaminergic derivatives of dioxolane:

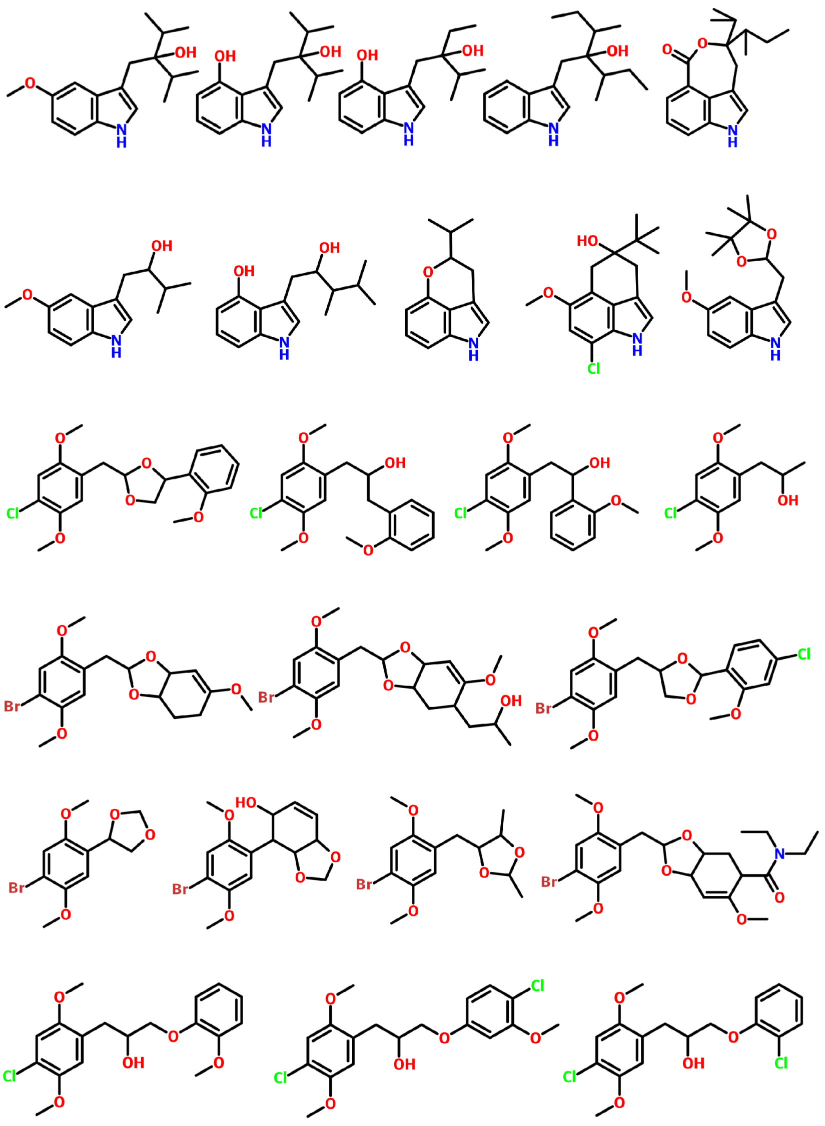


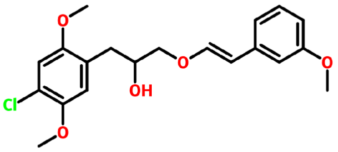
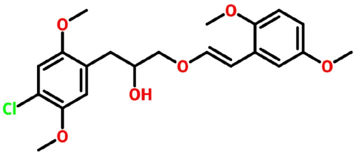
# Substituted structures tryptophol, phenylethanol, 1.3 dioxolane and other neutral compounds as structures that are close to nature of psychedelics.

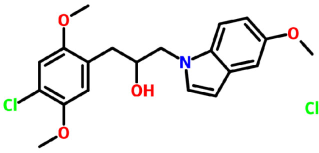
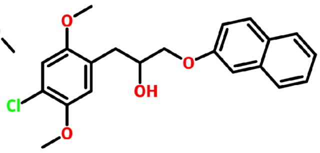
The aim of this work was to demonstrate an alternative structure of the alkaloids with possible potential as physiologically active substances.Since natural alcohols and other neutral substances have not been found among the natural psychedelics, in this work will be shown a chemical structure similar to the latter.

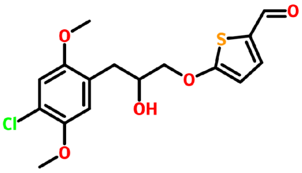
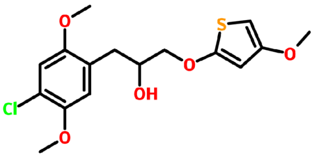
Compared to the already known tryptophol and phenylethanol, presented substances have a number of specific radicals and can be used to verify their psychedelic properties, in the search of new examples, new properties, to expand the list and other research.

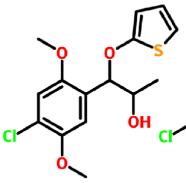
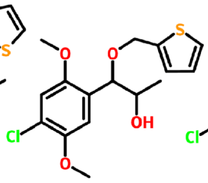
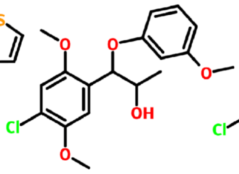
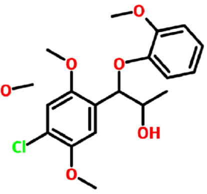
Illustration substituted structures:

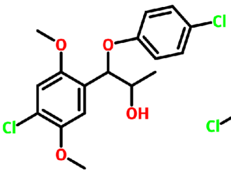
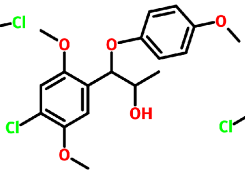
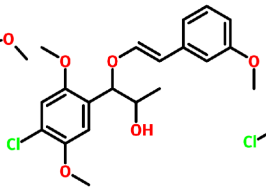
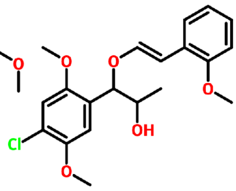


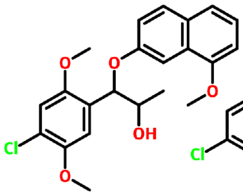
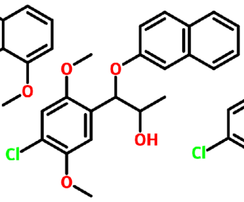
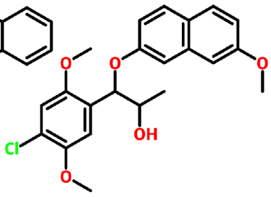
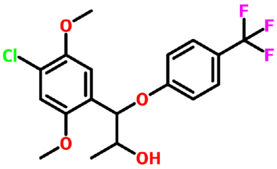



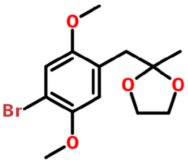
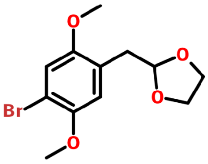
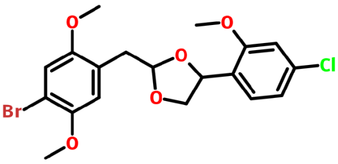



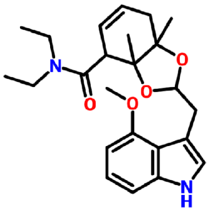
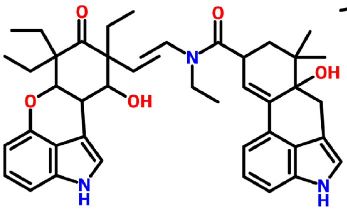
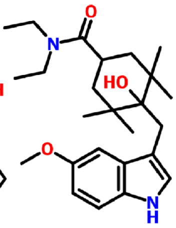
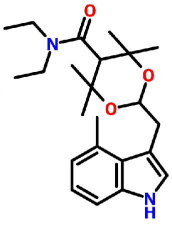



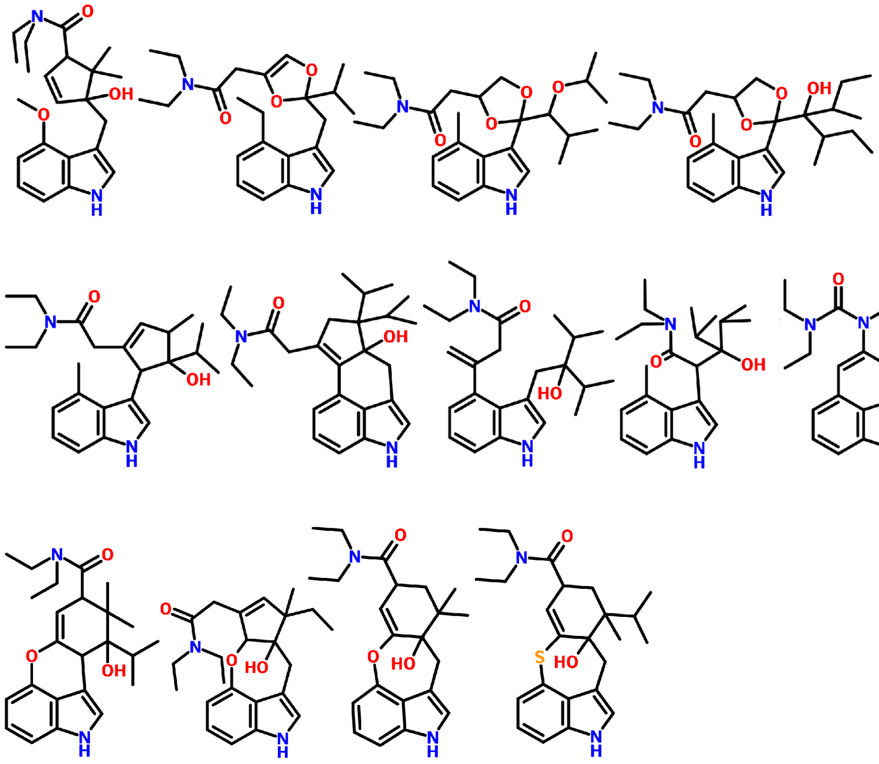







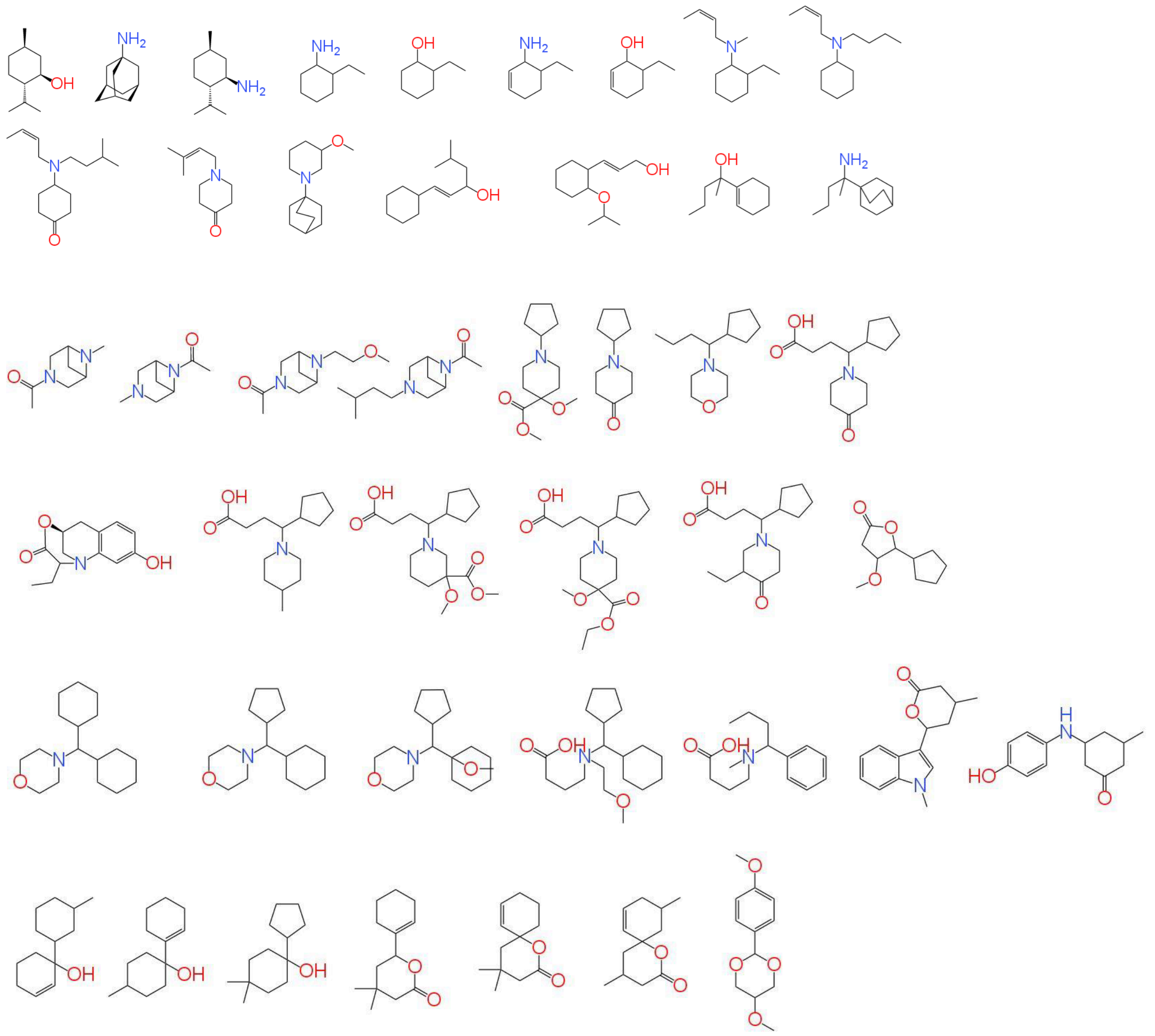
N
O
OH
O
NH
N
O
O
O
NH
N
O
O
O
O
NH
N
O
O
O
OH
NH
N
O
OH
NH
N
O
OH
NH
N
O
HO
NH
N
O
OH
NH
N
O
N
OH
NH
N
O
O
OH
NH
O
N
O
HO
NH
N
O
O
HO
NH
N
O
S
HO
NH

# Super light NMDA receptor antagonists as promising substitutes for Ketamine and Amantadine.

Kappa opiates, Ketamine and Adamantine are used as a tool for the relief of some neurological diseases, depressive disorder, to improve consciousness.. Although amantadine is a complex drug, such light, but more selective NMDA receptor antagonists can probably open the door to safer alternatives to ketamine, taking a step towards the correct medical use of kappa opiates. Is a super light kappa opiate possible? Yes, moreover, it is a publicly available terpene - menthol.

This work in the field of drug design demonstrates a wide range of possibilities for searching for such super light analogs, both in the world of alkaloids and their derivatives and synthetic amines, and in the world of terpenes and their synthetic derivatives and synthetic complex terpene alcohols.

The diagram demonstrates the diversity of nuclei suitable for searching for the desired drug, a wide range of physicochemical and pharmacological properties of candidates. The diagram displays a wide selection from elementary menthol derivatives to design at a new level of understanding in the field of kappa opioid construction:



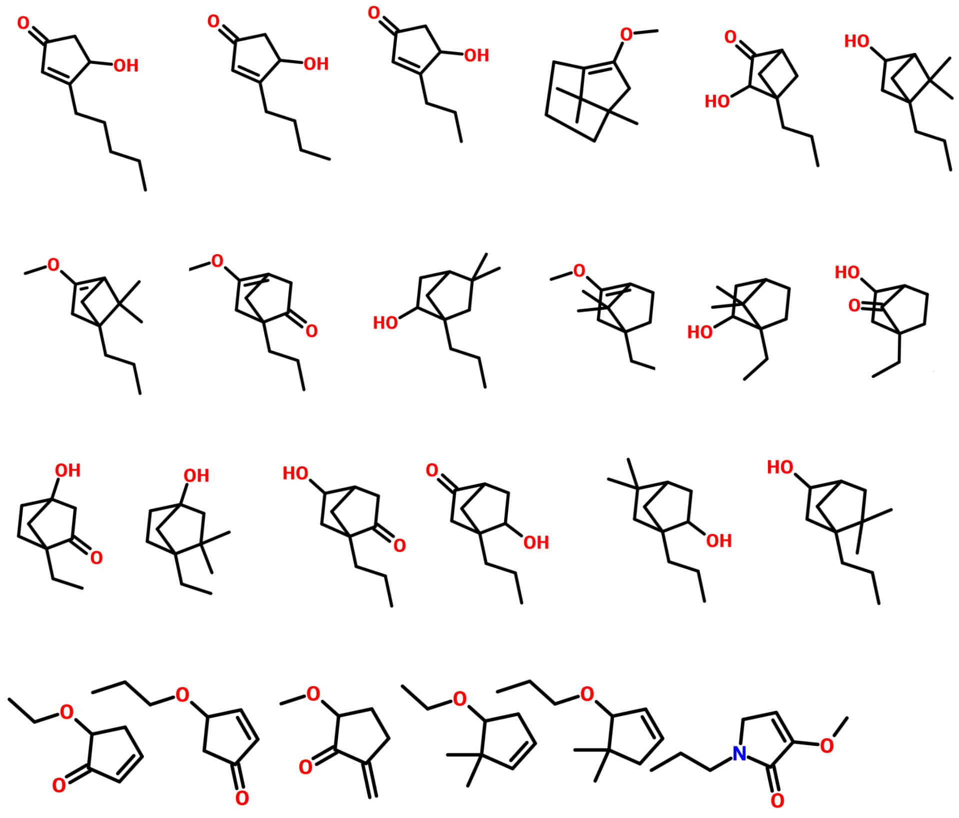
# Superlight synthetic cannabinoids.

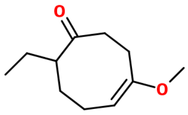
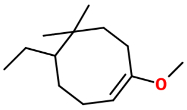
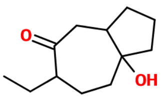
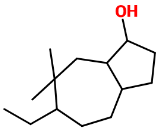
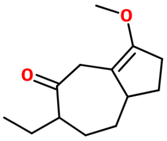
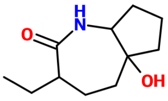
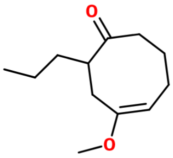
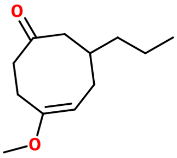
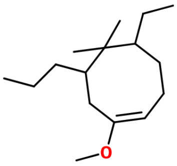
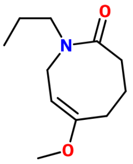
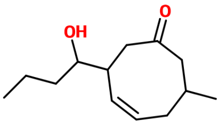
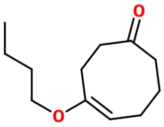
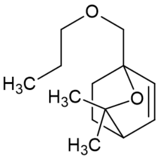
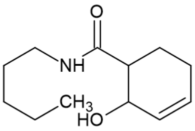
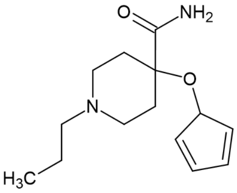
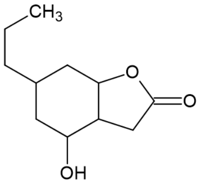
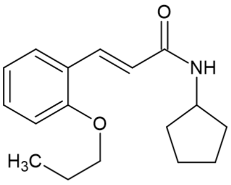
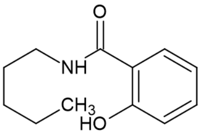
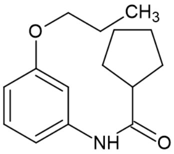
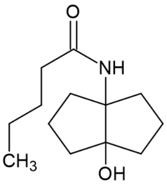
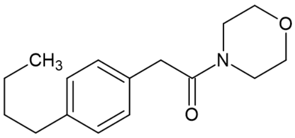
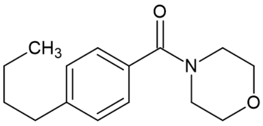
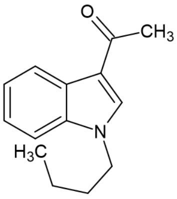
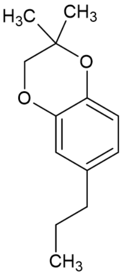
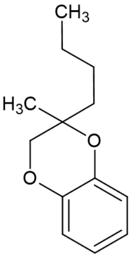
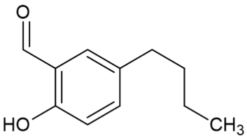
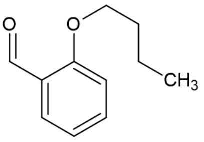
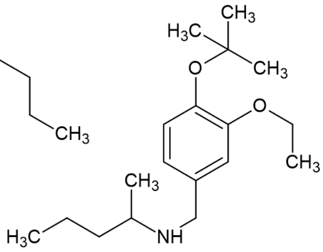
The structures are close to thujone, caryophyllene, and cannabinoids. Presumably, such chemical structures do not adversely affect the GABA brain system, as is the case with absinthe absinthe. Substances with exposure are lighter than marijuana, not hallucinogenic, not too psychedelic, with no noticeable effect on memory, probably have a very low ceiling of maximum activity and a large difference between the effective and lethal doses.

Such cannabinoids have a better chance of success when used in pediatrics, in the matter of legalization, because the lighter drug will meet less obstacles in the pharmacological market. Up to this point only powerful synthetic cannabinoids have been developed. Which in high doses have strong side effects. But there are no light drugs and this can probably be fixed.

Medical Marihua is very relevant today, but new varieties are not able to qualitatively change the properties of the drug. Without changing the structure of cannabinoid, we cannot achieve strong changes in the nature of the action. A directional design can provide many selective and fixed properties with particular limitations. This may be a new level of quality in such delicate areas as pediatrics and mass phenomena like legalization.

The figure shows examples of the possible construction of ultralight synthetic cannabinoids, recreational cannabinoids and medical synthetic cannabinoids:




O
O

O

O
OH

OH

O
O

H
N
O
OH

O
O

O
O

O

O
N
O

OH
O

O
O

O
H3C
H3C
O
H3C

O
NH
CH3
HO

O
NH2
O
N
H3C

CH3
O
O
OH

O
NH
O
H3C

O
NH
CH3
HO

O
CH3
NH
O

O
NH
CH3
OH

CH3
O
N
O

CH3
O
N
O

O
CH3
N
H3C

H3C
CH3
O
O
CH3

CH3
H3C
O
O

O
HO
CH3

O
O
CH3

H3C
CH3
O
CH3
O
CH3
CH3
H3C
NH

# Synthetic terpenes as a universal GABAergic, dopaminergic and light cannabinoids.

In contrast to glutaminergic terpenes, GABA activating terpenes are not represented in nature. Glutaminergic terpenes have a more destructive effect on the Central nervous system, however, included in the composition of the essential oil of Wormwood, Népeta catária and spices of Saffron - stigmas of Crocus Sativus.

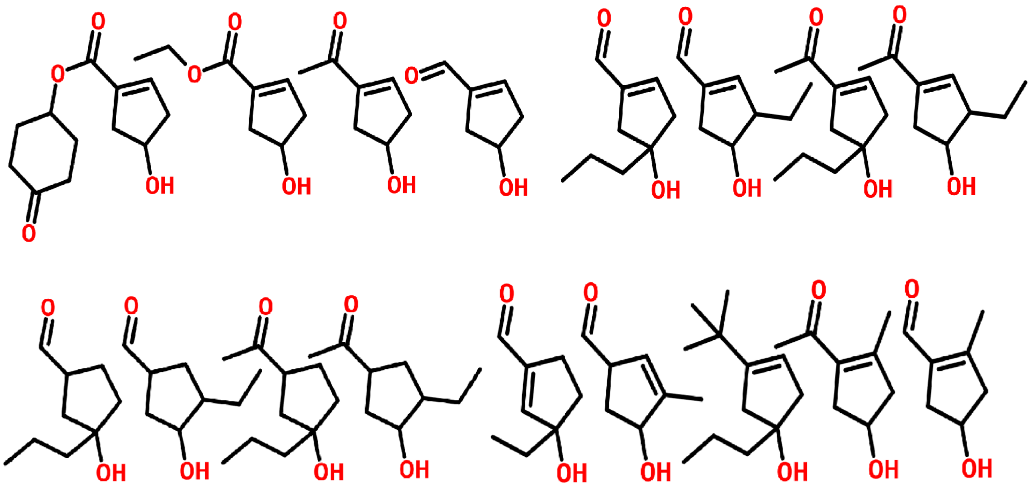
Structure of GABA and glutamic acid are close, and it would be logical to try to replace glutamic features with the GABA radicals. What was done on the example of the five-membered derivative of the aglycone picrocrocin (Crocus Sativus).

Also, given the possible recreational potential of such structures and some affinity for the anandamide fragment of such nuclei, pro-cannabinoid radicals were introduced into the structures, so that cannabinoids could receive a correction of properties on a completely new level. Design of multifunctional structures allows to obtain recreational substances with unique qualities, such substances may have a not-narcotic dopaminergic effect, limited GABA and pro-cannabinoid effects, with minimal risk of developing side effects characteristic of these groups..

Such substances may have great potential both in pharmacological practice and in recreational use. After all, being a lighter alternative to marijuana, pro-terpenes with modified properties, such as positive correction for dopamine, nootropic properties and pro-cannabinoid effects with a low ceiling of activity and subtle effects. Such substances may be a reasonable and safe alternative not only to hard drugs, but even to medical marijuana.

Also, some of the introduced radicals (butyl radicals) can cause pro-opioid mild mimetic effects to the structures, which together with pro-dopamine and GABA effects can complement the cannabinoid potential. Thus the cannabinoid profile is strongly modified by the positive influence of reinforcement neurotransmitters and can be unprecedentedly new on many deep levels of qualitative and quantitative changes.

Examples of some derivatives of terpenes:

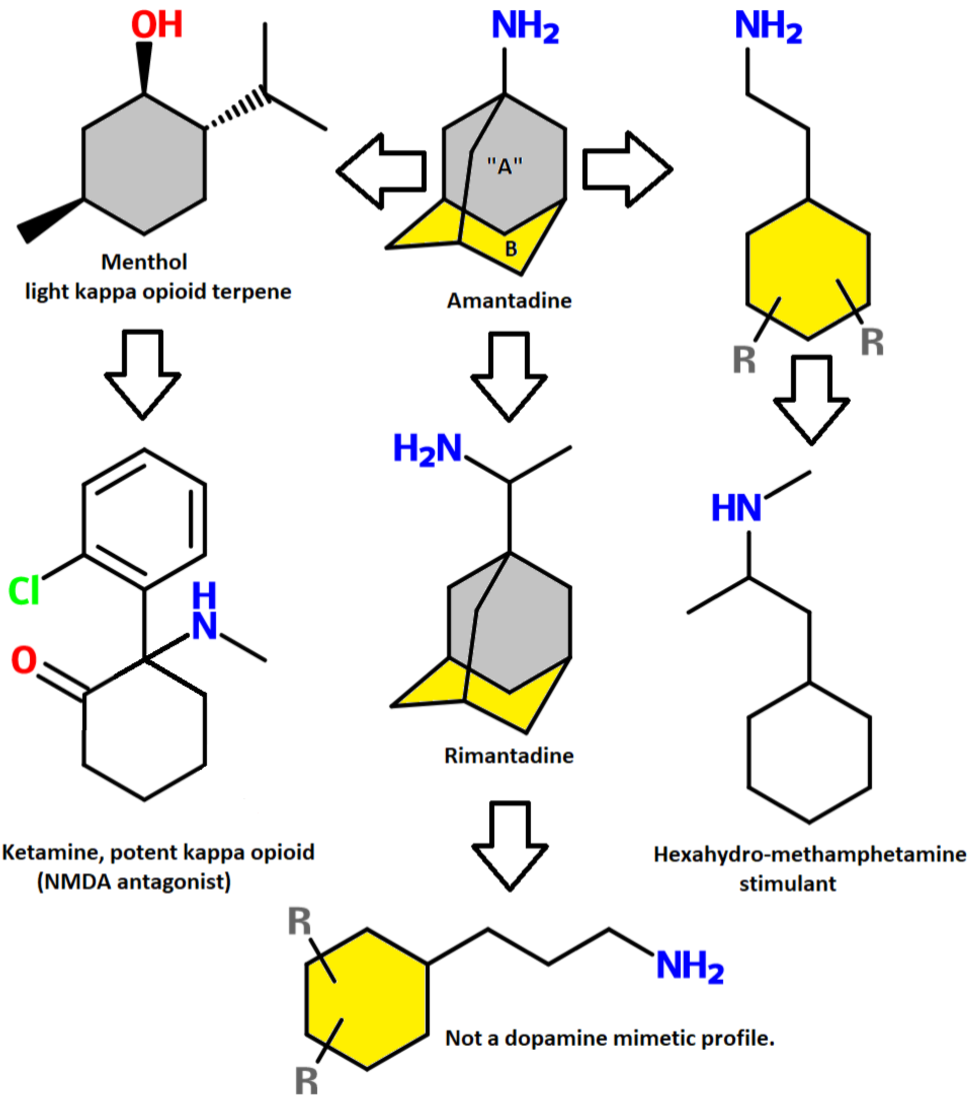


# The putative pharmacology of functional adamantane derivatives.

In this work, an attempt will be made to shed light on the drug design of a seemingly unusual nucleus - adamantane. On a closer look at this structure, you can see elements of rational drug-design, although the design of drugs in this group is likely to have irrational roots of bio-screening of chemical libraries.

This aspect is important in the context of the fact that pharmacology, as not an exact science, does not lend itself well to thorough analysis, but the tendencies in a more universal view of its branches are clearly visible, this is not a target, but an important enough message.

The work itself is implemented in the form of a diagram, for a more visual demonstration of the simplicity and elegance of a possible explanation:


OH
Menthol
light kappa opioid terpene
NH2
"A"
B
Amantadine
NH2
R
R
Cl
O
H
N
Ketamine, potent kappa opioid
(NMDA antagonist)
H2N
Rimantadine
HN
Hexahydro-methamphetamine
stimulant
R
R
NH2
Not a dopamine mimetic profile.

# Using water-based ultrasonic electronic cigarettes.

As is known, e-cigarettes have a number of fundamental disadvantages, such as the vapor containing some dangerous thermal decomposition products of the solvent, the lipophilic influence of the solvent and the pharmacologically poor composition.

Pure nicotine is deprived of the main carcinogens of tobacco smoke - nitrosamines and condensed aromatic smoke carcinogens, but pure nicotine may be less recreational and accordingly require a higher dosage, which will certainly affect the cardiovascular system, as well as toxicity.

Minor substances from fermented tobacco and tobacco smoke such as - cotinine, ethylnicotine nornicotine, isopropylnicotine and their pyrolysis products contribute to the overall pharmacology of tobacco products, enhancing the recreational qualities of tobacco products.

Cotinine promotes the release of dopamine, and when smoking cigars, large amounts of cotinine are likely to be absorbed in the mouth. The cigar has straight pores in which there is minimal reprecipitation of smoke, so that pyrolysis products and cotinine do not lose their activity and mostly leave with the smoke. Thus the quality of the recreational effects of the cigar can be mediated by a rich and correct ratio of pharmacologically active components, which is of course possible to simulate in other nicotine delivery devices, if we take into account this information and change the composition by adding additional ingredients to nicotine.

In addition to cotinine, additional ingredients may also be controlled by pyrolysis products of pure nicotine and cotinine, provided that small amounts of them do not compromise the safety of the product. Presumably, artificially created pyrolysis products of pure substances, under controlled conditions and with subsequent inactivation of active radicals (aging, humidity...), can be made extremely safe and added to the ingredients if necessary.

Thus, by improving the quality parameters, it is possible to create a safer and less toxic analog of tobacco products. Given that quality effects are the primary focus of recreational substances, it is possible that if quality effects are high, characteristics such as flavor and smoke are not primary and could be partially eliminated in favor of new delivery methods such as ultrasonic delivery of cold water vapor.

The flavor and smoky feel of cold water vapor is much less pronounced, but electronic delivery methods are widespread, and ultrasound-based nicotine delivery is the next logical step.

Also in favor of the ultrasonic delivery of nicotine is the fact that the tobacco taste can be molded with a flavoring agent, and flavors of a different nature, fruits, berries, flower compositions are also in great demand.

And so, electronic cigarettes have a number of disadvantages, having solved them, it is possible to move to a new level, after which it is possible to use a new delivery method, with minimal organoleptic flaws, but great quality advantages and possibly great potential.

The delivery of nicotine by the ultrasonic water-based method is a great opportunity to reduce adverse reactions and carcinogenicity, this is a new level of quality and control of the delivery process, and with a fairly revised approach to recipe development and a fine selection of ingredients, this is also a high recreational quality that is likely to keep the product on the market and compete with existing tobacco products.The recreational qualities of new nicotine delivery methods are key to positive change, as without competitive qualities such inhalers will not be able to make a significant difference in the market.

# Afterword:

Independent researcher, who is it? An unknown person, not a member of any organization, a scientist or a crook?

Maybe an independent researcher is a pre-institutional form of scientific activity from which scientific schools and institutes were formed? Maybe these are a few who gave rise to millions of qualified scientists, and the qualifications that they did not have. Maybe this is what was lost after the creation of a monopoly of scientific degrees. But the very foundation that created science was lost, in exchange for monopoly and structure, mass and control, control that destroys diversity. Can mistakes be made under conditions of total control and monopoly?

I had to write a book "Total Drug Design" in order to correct a number of errors and add missing links in theoretical and practical pharmacology. To give science a chance to absorb this data into civilization.

Pharmaceutical giants are part of a rather cynical world of business and modern science, and I will allow myself to ask a cynical question.

One person is capable of testing new substances on himself and developing theoretical pharmacology, discovering new types of physiologically active substances and optimal in-demand solutions for the production of necessary drugs. A single person is capable of developing projects with the potential for an annual turnover of hundreds of billions of dollars. A statement that requires not only proof but also refutation, are you ready to work a little on this, or you admit our own failure?

Where do independent researchers get their superpowers from?

Man is not a bearer of scientific data, he can only develop some high ability to read the surrounding world, which is science. A person, a group of people or a society have no relation to the real processes in the universe, except for those few that they can comprehend or with which they can interact. Monopoly in science belongs to the universe, and a conversation on the merits does not provide for a transition to the personal. Thus, we must exclude marginal patterns from scientific discourse, concentrate on the essence and achieve real goals.